Yellapragada SubbaRow

A Life in Quest of Panacea

An Album in Words and Pictures

Script by Raji Narasimhan

Designer: Narendra Srivastava

VIGYAN PRASAR

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Based on
In Quest of Panacea
Successes and Failures of Yellapragada SubbaRow by S.P.K. Gupta
in collaboration with Dr. Edgar L. Milford

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PREFACE

My first encounter, though virtual, with Dr. Yellapragada SubbaRow was as a student of chemistry in the Andhra University. To the boy of 14 that I was, the domain of chemistry was a Magic Kingdom, full of colour and power, awesome power indeed over nature but power in the service of mankind. I was convinced that the Magic Kingdom lay in the JVD College where the Department of Chemistry was situated. The college building with its rectangular clock tower itself inspired aura. To a contemporary of mine, who wrote an autobiographical novel, the rectangular tower clock with four faces was Chaturmukha Brahma, the four-faced Brahma. The main lecture hall of the Chemistry Department was a gallery flanked by a staircase adorned on either side by the portraits of great chemists. It was as if we were in communion with the gods themselves. In that pantheon of gods was Dr. SubbaRow. We were told that he made great discoveries in medicinal chemistry. However, unlike others in the pantheon, he was a strange god. For the excellent collection in the University library threw no light on him. He remained a mystery till two decades later when I chanced to come across a review in the *Economic Times* of a biography of Dr. SubbaRow by Shri S.P.K Gupta entitled ***In Quest of Panacea***. The review led me to the book. But for Shri Gupta, Dr. SubbaRow would have continued to be "a gem of purest ray serene" that "the dark unfathomed caves" of Science bear. All of us owe an immense debt of gratitude to Shri Gupta. Against heavy odds and with missionary zeal, Shri Gupta has been striving to secure for this great son of India his due recognition in his native land. Earlier discoverers of antibiotics like Fleming, Chain and Florey for Penicillin and Waksman for Streptomycin won Nobels. Had Dr. SubbaRow, who gifted the tetracycline antibiotics to humanity, secured a Nobel Prize like them, Shri Gupta would have lost his mission.

This book is in a sense a companion volume to the biography. It deals with the work as well as the life of Dr. SubbaRow though with a greater emphasis on the life. These are days when several Indians have scaled great heights of achievement in the United States in several fields like business, academia and Government. However, they face far less odds than pioneers like Dr. SubbaRow and Kolachala Seeta Ramayya. And yet the record of Dr. SubbaRow has been rarely equalled. For he rose to be, in October 1942, Director of Research of Lederle, the pharmaceutical division of the chemical giant American Cyanamid, and guided its R&D efforts till he died in harness in August 1948.

While the scientific contributions of Dr. SubbaRow are now quite well known and lauded, SubbaRow the man is still a mystery. Shri Gupta needs to be specially commended for his efforts to unravel the mystery.

Who was SubbaRow? What was his Being? What did he become? Why did he become what he became? These are interesting questions: a clue to these is provided by the two letters on religion published in the volume. Dr. SubbaRow defies all classification. He was a scientist, a philosopher, a spiritual man in search of 'fame' who was constantly unravelling the mysteries of nature but without losing focus that discoveries are to be

pursued to improve the lives of the people and not for commercial purposes. Through science he tried to establish a relationship with God and his fellowmen. What makes him a unique personality was his approach to the pursuit of knowledge. He explored and sought knowledge for its own sake and not as a means for personal achievement or glory. Scientific reasoning and observation to him were not merely the tools of his experimentation to transcend nature; they were also the means to undertake a journey into his inner self.

His relentless urge to seek knowledge led him to many important research discoveries in medical science. Yet, when it came to claiming the credit, he preferred to receive it as the collective effort of a team. This sense of submerging the individuality without any remorse was his own way of stating that man relates not only to God but also to his fellowmen. Remarkably, he practised these virtues in a foreign land amidst a culture which takes pride in individualism and its rewards. This speaks of his upbringing and his sense of conviction in the values he imbibed in his childhood.

Dr. SubbaRow believed that the scientist's creativity and originality flow from the freedom of thought enjoyed by him. Nevertheless, he was acutely conscious that this freedom of thought can also lead to dangerous temptations of power and self righteousness. The only way these temptations can be avoided is by subjecting the creative thought to the discipline of prayer. He was a true agnostic in his pursuit of knowledge and yet he was very clear that knowledge is ultimately a tool for the service and benefit of humanity and not for self-glorification.

Dr. SubbaRow's impatience with life is manifested in his seemingly whimsical switches of interest before ever consolidating his gains in whatever he did. Apparently, his restlessness reflects a genius that wanted to accomplish much more than what was physically possible. He did not want to be part of a rat race. Though essentially a religious person, he considered religion to be a dynamic subject rather than a static code of established principles. He was a visionary who wished to be a perfectionist both in his science and 'self' but did not want to accept the established principles and codes as a given truth. He desired to experience and experiment at every stage: "I am too restless to be able to say what my views are or even to promise they will be my beliefs in the next one year. I have to work them out in my own way. Listening to the views of all of you and trying to integrate them into one whole. I suppose even then I will only approach and never arrive."

The life of Dr. SubbaRow is an example of how religion and tradition need not necessarily be incongruous and incompatible with the scientific temper, also of how they can foster modernity and development. Dr. SubbaRow is an anachronism in today's world which is more intensely individualistic than the world in which he lived and excelled.

Dr. R.V Vaidyanatha Ayyar

FOREWORD

The Publication Programme of Vigyan Prasar has taken some shape in the last few years. To start with, Vigyan Prasar brought out a number of publications on a variety of topics of science and technology on an experimental basis. Popular Science classics, India's Scientific Heritage, Natural History, Health, and Do-It-Yourself are some of the series that evolved over the years. Our emphasis has been on bringing out quality publications on various aspects of science and technology at affordable prices. Further, Vigyan Prasar is putting in efforts to bring out publications in major Indian languages for various target groups.

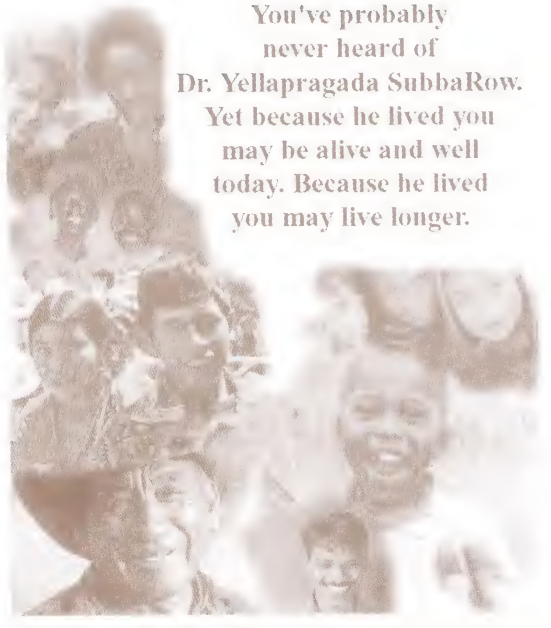
The present book *Yellapragada SubbaRow: A Life in Quest of Panacea* is about a great life in science. SubbaRow is one of those few individuals who toiled and struggled to achieve seemingly impossible feats. His life is bound to inspire the youth to take up challenges and to rise above mediocrity. SubbaRow was the man behind development of many wonderful life - savings drugs—antibiotics, vitamins and so on. He worked on fundamental concepts in biochemistry. His interest was not confined to scientific research alone. He was a great adventurer. He tried his hand at many diverse things.

We are thankful to Shri S.P.K. Gupta for helping us in bringing out this volume. Shri Gupta has made sincere efforts in spreading the message of SubbaRow's life through various means. The present book is based on an earlier book *In Quest of Panacea: Successes and Failures of Yellapragada SubbaRow* by Shri SPK Gupta in collaboration with Dr. Edgard L. Milford. The text of the present book has been written by Raji Narasimhan, a well-known novelist. We do hope the book is received enthusiastically. We are grateful to Dr. R.V. Vaidyanatha Ayyar for writing the Preface.

New Delhi
Feburary 14, 2003

V.B. Kamble
Acting Director
Vigyan Prasar

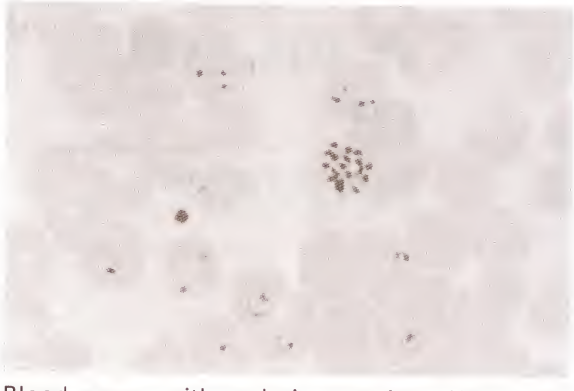
A VICTIM OF NAIVETE



DORON K. ANTRIM : Miracle Man of Miracle Drugs
ARGOSY, April 1950

Why is Yellapragada SubbaRow not an icon figure in medicine in the way that Subrahmanyan Chandrasekhar is in astrophysics or C V Raman in physics or Srinivasa Ramanujan in mathematics? The credentials are there, impeccable, renewed and reauthenticated time and again.

As recently as the foreign intervention in East Timor, in the last years of the century just gone by, Doxycycline was one of the drugs included in the medicine-cum-survival kits of the UN Assistance Mission. It was protection against malaria. Doxycycline is the third generation tetracycline (broad-spectrum antibiotic) to enter the world medical market since the advent of Aureomycin, the mother of tetracyclines, fathered by SubbaRow. From the manipulations and modifications of its molecule by chemists, varied new tetracyclines have poured into the market, enhancing the portfolio of cures in the hands of doctors. In the plague epidemic that broke out in 1994 in Maharashtra and Gujarat, tetracyclines contained and eradicated the disease. Again, folic acid, the anti-sprue remedy synthesised in 1945 under his research direction, has had a sustained and widening sphere of use. It is effective in various



Blood smear with malaria parasites: Unlike the traditional chloroquine and the new drug, mefloquin, doxycycline is the least toxic. (Photo: World Health)

kinds of anaemia, in addition to sprue, and helps fight heart disease by reducing the levels of homocysteine in the blood. So too with methotrexate, an anti-folic conceived of by the same imagination that begot the folic vitamin. It is not only used in childhood and adult cancers for which it was originally devised, but also in rheumatoid arthritis and psoriasis. Of late it has taken in its stride medical abortions of ectopic pregnancies. Most recently, when given in low dosages, it has been found to reduce the use of steroids in asthma patients.

SubbaRow's drugs thus have not by any means become obsolete or defunct. Their relevance continues and, if anything, increases. Yet, his image and persona are not evoked at the mention of any of his drugs in the way, for instance, that the mention of penicillin evokes the image of Alexander Fleming.

The reasons for this shadowy quality to his life lie more in his own make-up and temperament than in the machinations of jealous colleagues. Very early in life he made a statement about his aims and aspirations, which makes interesting study in the full context of his circumstances then, and the events of his life later.

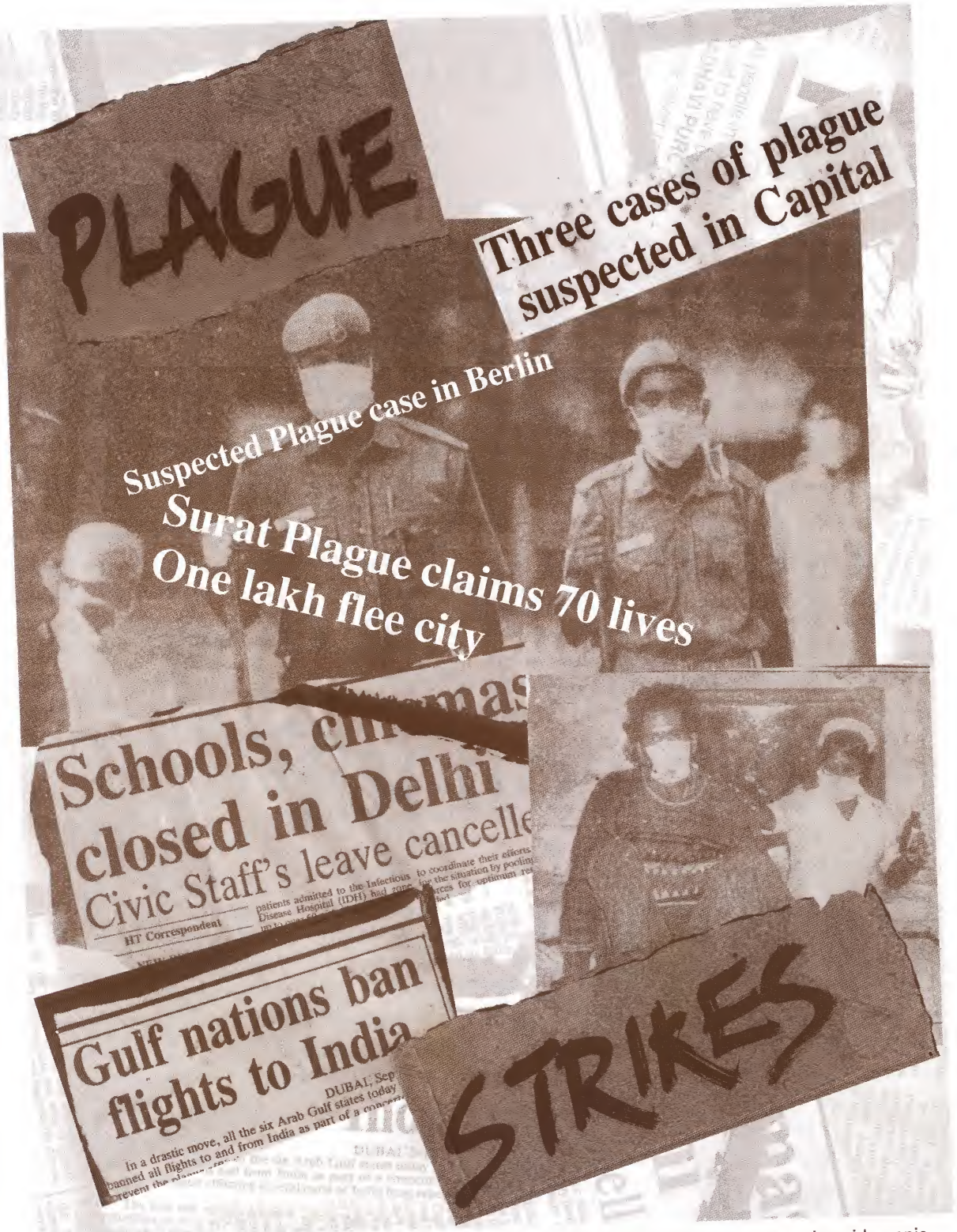
'I must win a name in the world. Then only would life be worth while', he said, speaking to his mother Venkamma. Like all mothers, Venkamma was given to crystal gazing about her son's future.

He'd just finished intermediate college, with distinction in mathematics. Common sense and practical wisdom dictated an intensified pursuit of mathematics, cashing in on the talents given to him, and thereby escaping the morass of poverty in which he was mired. But his own meaning of 'winning a name' was not so simple and direct. He had a long-term plan, that of joining the Rama Krishna Mission as a sanyasin. Venkamma had already vetoed it. She had fiercely refused her signed consent, which was a necessary formality. However, he was going to realise his goal by going in for medical studies, then joining one of the clinics of the Mission, and working his way round from there to the monastic order of the Mission.

Later, he was to give up the idea of monk - hood and opt fully in favour of medicine as more tactile and immediate than the stern abstractions of the ascetic path. But the point is that his meaning of 'making a name' contained in its folds the ideal of self-effacement which is common to the life of a sanyasin as well as a life devoted to healing the ailments of fellow men.

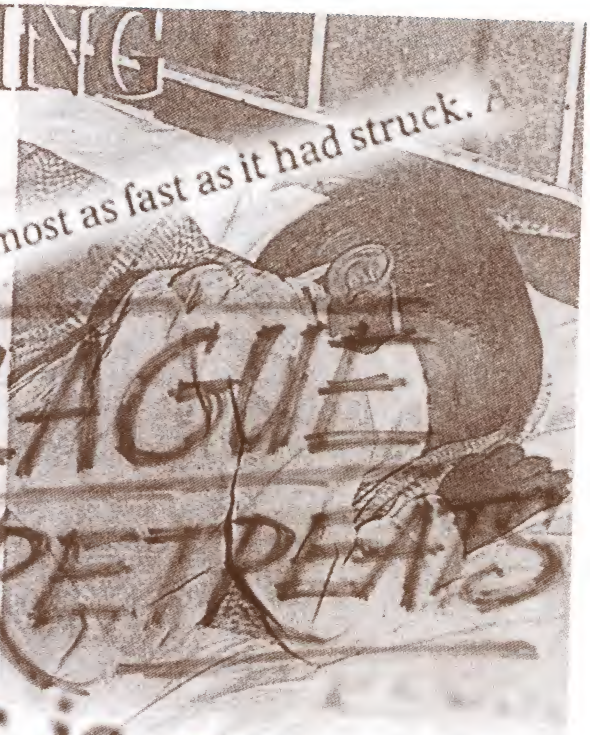
It was fatal naiveté. One of the strategies of winning fame is self-projection, in stark contrast to self-effacement. The fame-hungry man or woman is narcissistic, compulsively so. He builds

Anopheles mosquito: Vector of malaria. Doxycycline taken 12 hours before exposure gives protection from infection.



Plague strikes : Newspapers reflect the initial terror struck by the 1994 plague and the nationwide panic.

THE MORNING AFTER



As the epidemic subsid... of rumours ... but there are more ... have to be tackled.

By KAI FRIESE

THE panic evaporated almost as fast as it had struck. As ... laboratory-confirmed cases began to re... figures of 'suspected cases' as the index of ... alarm, things suddenly began to look quite ... Bombay luxuriated in the fact that two weeks after the ... began, no cases had been confirmed in the city. Even in Surat, ... had been admitted to the Civil Hospital since ... being treated by October 8, ... suspected ... seemed to take ... toll from the police firing ... outstripped the day's plague deaths, ... arithmetic was plainly encouraging and by October 8, ... hours had passed without any death being reported. Three ... weeks into the epidemic, the dreaded plague had cost just 56 ... lives—a tiny fraction of the annual toll of some of India's more ... chronic public ... afflictions. ... was obvious among health ...

"... the war is over."

Who won it?

A plague patient at Delhi's infectious diseases hospital

... situation is well under control," said Delhi's Health ... Harsh Vardhan, "by the end of the week there ... few stories about the plague in the papers." And ... Dr N.K. Shah, WHO's representative in India, ... satisfied, the war is over."

... it is a different matter. Perhaps not the plague ... bacillus, though it had exacted a terrible ... in death, human suffering and, of course, ... disruption (*see accompanying story*). ... last India's latest tragedy as a ... with administration will ring ... hero. if there was one, was the ... tetracycline, which, ... design, was still in sufficient ... although it was on the brink of ... harmful varieties of micro-organ... apparently developed resistance to it. *Yersinia* ... thankfully, has not. Nearly half a million capsules ... of the drug were distributed in Surat alone, and they clearly did their work. Similarly, the very panic that spread the pneumonic plague from Surat finally helped ... to report to their ... mopping up ... drives and the ... enthusiastically ... the most literal ... additional 500 ... into service and

Suspected and confirmed cases : The numbers shrink

	Confirmed	Death toll
Rajasthan	245	52
West Bengal	23	3
Haryana	5	
Andhra Pradesh	3	
Maharashtra (Bombay)	119	

'Doxycycline better for treatment'

'The real hero, if there was one, was the 40-year-old antibiotic, tetracycline.'

Tetracycline is India- born doctor's gift

Clippings by S P K Gupta; art work by Muthu Koya

an image of himself, consciously fosters it, even when he seems to be cornered, seems helplessly responding to nosey newspapermen. Like a virus implanting itself into the organism, the aspirant to fame implants his image into the public mind, where it floats up to the upper layers of the public consciousness at various god-sent and contrived opportunities.

SubbaRow was incapable of such indulgence of the self. For him the self was finite. It was valid only to the extent that it woke one to terrains beyond. At all the decisive moments of his career, this attitude of more-than-the-self took over completely, handicapping him in the dog-fight-dog world of competition and one-upmanship. When Aureomycin was to be presented to the New York Academy of Sciences, he left the task of presentation to Benjamin Duggar, his plant physiologist. Duggar had undoubtedly made a key contribution to the project by the painstaking job he had carried out of screening thousands of moulds for extracting the antibiotic. But the final choice of the mould, A-377, from among the hundreds he isolated, was the decision entirely of SubbaRow and the bacteriological group directly under his supervision. Duggar made no mention of the bacteriological or the chemical and other groups whose dedication provided solid foundation to the Aureomycin work. He got away with it because of SubbaRow's innate preference for the quiet of the shadows to the din of public acclaim. All the top newspapers of New York City had stories from their science correspondents singling out Duggar as the brain behind the discovery of Aureomycin. The other members of SubbaRow's team, however, were not so passive. They evened the score by relegating Duggar's work to footnotes in their publication, months later, of select chemical data in *Science* journal.

But the point is that in none of the records does SubbaRow come out as the director par excellence that he was of the Aureomycin project. Patent attorneys talking to the members of the project could see clearly how important SubbaRow's work had been, but found little written evidence of it. He just never signed his research notebooks.

It was the same with folic acid. Extracting it, first from pure sources like liver, then from fermentation broths for greater quantity and finally resorting to synthesis for viable commercial production, he captained the work and the team under him with magnificent grasp of all the chemical, isolation, technical and human aspects of the project. He was the brain, the mastermind, behind it. But he didn't, once again, personally make the formal announcement of it to the assembly of experts called for the occasion. He chose for the task, Professor W. H. Peterson of the University of Wisconsin's Department of Biochemistry. The reason for his choice was of symbolic significance. The symbolic was prized by him as much as the effacement of the self, the overt and the intrusive. It was in Professor Peterson's laboratory that the discovery was made in 1944 of *Lactobacillus casei* which speeded up the isolation of folic acid. In entrusting to Peterson the task of formal presentation, therefore, he was making a civil gesture of reciprocation.

And once again, this impersonal, pluralistic approach cost him the exclusive attention he deserved, and would have welcomed if 'winning a name' meant to him what it meant to most people.

It didn't. Achievement never meant for him any blow-ups of individuals into personalities. The individual for him was fluid substance, to be absorbed into the heat and press of the collective. Ideas, thus, never were seen by him as any one's exclusive preserve. They never became 'intellectual property' carrying rights of ownership. This principled impersonalism often ruled out for him easy ways out of professional tight spots. When he was working out an alternative process of synthesising thiamine, for instance, a New York company offered him the services of an ex-chemist of Merck, experienced

in thiamine synthesis. Their conditions were that any process resulting from the chemist's ideas during his tenure at Lederle would become their (the NewYork company's) property, to be patented at Lederle's expense. In return Lederle could have an option to exclusive license at 5% royalty. What were 'his ideas', SubbaRow wanted to know. The ideas of Lederle's men may have originated when they worked somewhere else, and likewise the ideas of the chemist proposed to be loaned to him probably had their origin at Merck, or elsewhere. Ideas had ancestry, had lineage, but did not have identifiable parents, he said. The offer of the New York company was, of course, turned down.

Again, when difficulties cropped up earlier at Harvard over the promotion of his associate and co-researcher on the phosphocreatine project, Cyrus Hartwell Fiske, as department head, SubbaRow smoothened the way for him by disclaiming any credit for phosphocreatine. He wrote a letter to this effect to James B Conant, President of the University. With Fiske, his relationship from the very beginning of his Harvard years had been governed by scruples that verged on the traditional. Fiske was his elder, not perhaps by age, but by the kind of experience that counted in University faculties. He was a brilliant ex-student of Folin, the Head of the Biochemistry Department. SubbaRow's own experience as vice principal of the Madras Ayurvedic College slid to second place against this. SubbaRow acknowledged almost instinctively the edge that Fiske enjoyed. It is as the Fiske-SubbaRow (not SubbaRow-Fiske) method of estimating phosphorus content in blood that his process has gone on record. This antecedence of Fiske found ready acceptance in SubbaRow's book of shoulds and should nots. Principle and practical sense existed together for him in an innocent, very Eastern conjunction. In his letter home after the announcement and acclaim of the Method, there is a shy assumption by him of exclusive authorship of the Method. It is couched in these words: 'I worked under the supervision of Dr Fiske, and it is courtesy in research that both names should go to the Method. Moreover, a method bearing the name of one with a big reputation like Dr Fiske's would be entirely genuine rather than one bearing the name of a novice unknown to the scientific world. So this method is named "Fiske-SubbaRow Method of Estimation of Phosphorus" ...' (!)

When he disclaimed any credit for phosphocreatine, he perhaps expected, by the same logic of innocent hyperbole prompting his disclaimer, Fiske would protest against his disclaimer in equally hyperbolic terms of outrage and upsurge of brotherly love, thereby setting the record straight as far as his own merits were concerned. This did not happen. Fiske made no graceful counter disclaimer. Nor was Conant, the president of Harvard University, roused by any curiosity about such a letter of disclaimer from a person well acclaimed in his field. The official seal of approval thus came down with finality on SubbaRow's letter. And with it the doors were closed for his own promotion in the faculty. For,

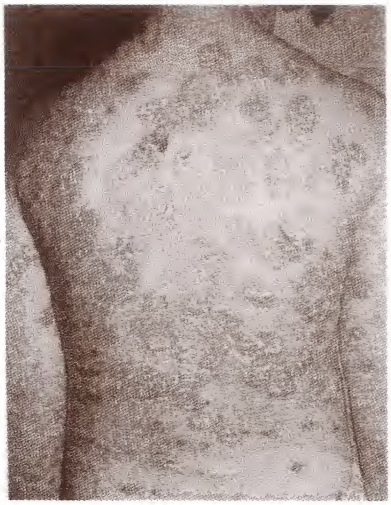
Malaria Patient : Doxycycline, Third generation successor of SubbaRow's tetracyclines, has been cleared by U.S. Food and Drug administration for prophylaxis of malaria, especially of the malignant variety caused by Plasmodium falsiparum (source : Internet)

Conant reasoned, why should a man who was second fiddle on his own admission be given higher posting?

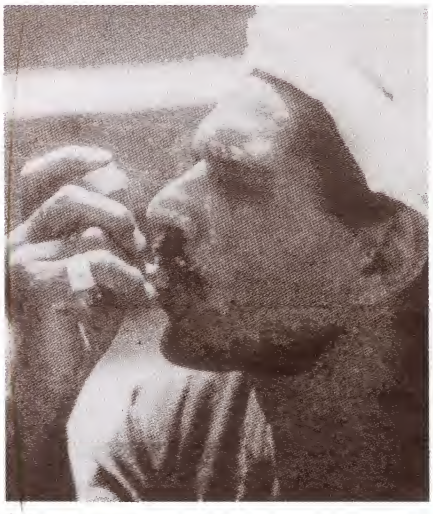
SubbaRow never learnt the ruthless ways and crass egocentrism of competition. At the end of every achievement he always woke to the smallness of the fruits of human ingenuity, a smallness set off by the vast realms of what he felt wasn't just the unknown, but was probably the Unknowable. Achievement made him reflective.

It made him impatient to reach for the next milestone, probe farther the enigmas of the Unknown. He simply didn't have the time to be pleased with himself, bask in self adoration. He simply didn't have what it takes to be famous, just didn't have the necessary killer instinct. He was not destined to be famous, no matter how solid and enduring his achievements

Hands of a rheumatoid arthritis patient: Methotrexate is a fairly standard drug in the treatment of rheumatoid arthritis. (Photo: World Health)



Patient with psoriasis, a skin condition amenable to treatment with methotrexate. (Source: Medical brochure)



Asthma patient using a steroid spray. Methotrexate can reduce steroid dependence and hence its complications. (source: Glaxo and Wellcome Business Review 3 (1999:1)

Signs and Portents

Umamaheswara Temple on River Godavari at Kotturu Jagannadhapuram, the ancestral village of the Yellapragadas in Andhra Pradesh.
(Photo: S P K Gupta)

SubbaRow was the fourth of seven children in a family of impoverished Brahmins.

Brahmin poverty has a touch of irony to it, unlike the poverty of other deprived sections. For it is poverty of only money and this lone lack stays like a blight over solid, grassroots riches, stifling their action.

There is education in brahmin poverty, for instance. There is a strong bent for the written word, a thirst for the wisdom of minds past, stored in palm leaf or papyrus. There is faith in the future, which is reflected in a desperate, forward-looking temper striking away from the want and ache of the present. Add to this a strong sense of lineage and ancestry, the sense of a past remembered with pride: one gets, then, an idea of the canvas and time-space on which the consciousness of the impoverished Brahmin operates.

SubbaRow's forefathers were Niyogi brahmins. Yellapragada, the prefix to his name, denotes descent from Yellanna, who was a preggada or minister in the royal court of the Nawab of Golconda in the seventeenth century. The Yellapragadas served as Karanams or revenue

Niece Saraswati at the ancestral well in Kotturu Jagannadhapuram whose karanamship grandfather Subba Raju gave up along with the land that went with the job as village accountant, to his brother, and moved to a town where his two sons could get modern schooling. (Photo: S P K Gupta)

accountants of Kotturu Jagannadapuram, three miles east of Mukteswaram on the river Godavari in the present state of Andhra Pradesh, down to the 19th century.

The decline of the family started from the time of SubbaRow's grandfather, Subba Raju. The lands that went with the accountant's position no longer sufficed for his growing joint family.

Subba Raju, thus, migrated to the town from the village. Of his two sons, Jagannadam, SubbaRow's father, survived, and married Venkamma, the sister of his first wife who died early. Of his family of seven, SubbaRow was the fourth.

Jagannadam was unlucky in both health and service. His health forced him into premature retirement from the provincial revenue service where he had a post. All through the years of his stay in the country, till he set sail abroad and touched American soil in October 1923 at twenty-eight years of age, SubbaRow's life was a saga of chronic and many-sided insecurity. There was the basic insecurity caused by his father's joblessness, failing health, and the penury these bred. But worse was the insecurity bred by his mother's domineering ways. These rose partly from her own nature, no doubt. But they were also outcrops of her desperation at a non-functioning bread-winner. Maternal domination resulting from paternal ineptitude can be a crippling experience for a growing boy.

His years from his school days onwards were years of attempts at breaking free of the prison called home, and the prison warden, who was his mother.

His first escapade occurred when he was 13.

Along with his cousin, Venkataramayya, he decided to run away to Varanasi and 'live easy' by selling bananas to pilgrims. Or perhaps they could coach backward students? SubbaRow gave free rein to fancy, leaning against the prow of the boat. The

Nadimpally House, Bhimavaram: SubbaRow was born on January 12, 1895 in this modest house rented by his father while head clerk in the *taluka* office.
(Photo: S P K Gupta)

Girls' School at Narasapuram which SubbaRow attended with his sister Annapurna to begin his education.
(Photo: S P K Gupta)

cousin was more subdued, daunted by the dark boat. They had 36 rupees between them, left over from the sixty rupees that had come from Venkataramayya's father that morning. Two half tickets to Nidadavolu, which was the rail head, had cost them Rs.12 each. Venkamma's men caught hold of them two miles from Nidadavolu, and brought them back, where a sound thrashing awaited our scientist.

Venkamma was determined he would complete school. In the meantime his father was invalidated by beriberi, which put an end once and for all to his sporadic efforts at finding a job. The family moved to Modekurru, to the house of Venkamma's widowed sister, Balamma.

Yellapragada Venkamma

It was back to school for our scientist, more unwilling than ever.

He failed his matriculation twice. And other influences worked on him further undermining his doddering scholastic efforts.

His brother, Purushottam, to whom he was sent after his first failure in matriculation, transmitted to him all his own nationalistic passions. Purushottam himself had paid dearly for them. He'd participated in the national movemnet against the Partition of Bengal. For this he'd been expelled from college. He had had to do his M.A and LL.B from distant Allahabad, and had not got anything better in life than his school teacher's job in the Viresalingam Theistic High School at Rajahmundry.

A second, and greater, influence on SubbaRow was that of the poet Chilakamarti Lakshminarasimham, who communicated to him his reformist zeal of a Hinduism shorn of ritual and orthodoxy.

A boat is dragged on the placid canal waters by pullers walking along the bank near Palakol. SubbaRow used such a boat to reach the railhead in his bid to run away to Varanasi with dreams of striking it rich selling bananas to pilgrims. (Photo: S P K Gupta)

Aunt Balamma's house in Modekurru where SubbaRow spent a part of his boyhood after the family was forced to shift there by his father's premature retirement from government service. (Photo: S P K Gupta)

All these were heady counter influences on a boy already wavering in his loyalty to studies. He failed his matric again. On blistered feet, under the hot sun, he trekked back 25 miles to his mother's home at Modekurru. An angry and doubly determined Venkamma now sent him to Madras City to the Hindu High School at Triplicane. Two months before the exam, his father died. He came back home for the last rites. His train fare back to Madras and the expenses for his remaining two months at school came from the sale of the odd bits of jewellery still left to Venkamma.

In his third attempt he passed.

And now, as a poor and lonely college student SubbaRow was more than ever assailed by ideas of right action, the right motives for action, and the right ends in life. He wanted to choose well, in full, honest accordance with his innermost desires, and thus avoid unhappiness later. His soul searchings did not yield him a single course of action he could consider untouched by self indulgence or maya. Whether politics, or medicine or the nobler-seeming motives of patriotism and humanitarianism, all seemed to him world-centred and illusion-fomenting.

What could be the right motives of action for a man? Vanity? Self-gratification? Or was it the life of the spirit?

It was the last, he felt certain. He felt called to the sanyasin's life. Even doing good to others was an act of self-gratification, he reasoned. He turned to the Rama Krishna Mission. The recluse's life attracted him. Venkamma's badgering at him to make good and make her a proud mother, thereby compensating her for the proud wife his father had not made her, only drove him to question her values more.

The swamins of the Mission put him through a course in comparative religion before considering him for their order. SubbaRow walked three miles every morning and evening to and from his room in Triplicane and the Ashram premises on Brodie's Road at Mylapore. There, he studied the scriptures of all religions, learnt yoga, and the ancient art of astrology. With all these intense, non-collegiate labours, he ought to have failed in his college exams. But a piece of cold reality intervened to thwart his romantic, even if carefully laid, plans of joining the swamins of Rama Krishna Ashram. This stark piece of reality was that his expenses would not be met indefinitely by his roommate and provider, B. Narayanamurty, if he flunked his exams. The exact nature of his arrangement with Narayanamurty is not known. But the point to note is that it made him bone up on his text books without further ado. He passed his Intermediate

Taylor High School at Narsapur: Resentful of mother Venkamma's authoritarian ways of instilling education, SubbaRow often played truant, was once struck off from the school rolls; re-admitted, he made an abortive escape to Varanasi. (Photo: S P K Gupta)

The Veeresalingam Theistic High School, Rajahmundry (entrance gate): SubbaRow imbibed the patriotic spirit of brother Purushottam, a teacher at the school, the zeal of social reformer and poet Chilakamarti Lakshminarasimham, who lived next door, and got involved in the intellectual ferment of the city. All this left him little time or inclination for studies, and he failed again in the matriculation examination. (Photo: S P K Gupta)

exams. He got a distinction in mathematics, in no other subject. Pressures mounted on him now to take up mathematics honours as the logical next step.

He didn't wish to. And to make matters worse, the Rama Krishna Mission said it wouldn't take him into its monkhood without his mother's written permission. But it persuaded him to take up medicine as a career. As a medical graduate he could hope for a place in the network of medical relief and care that the Mission ran.

He joined the Madras Medical College in 1915. But the Rama Krishna Mission was the true steering force of his actions. Naturally enough spiritual ideals and queries kindled afresh in him relegating studies to the background.

This time his soul searchings yielded some important leads for future courses of action. He realised that Advaita, the philosophy of Sankara, that defined the Rama Krishna Mission's corporate identity, could not be any spur of action for him. He could not dismiss pain as maya. Pain, whether physical or emotional, was a positive event. It required an equally positive response of countering or alleviation, or at least an attitude of concern.

Hindu High School, Chennai: SubbaRow passed his matriculation examination from here after failing earlier attempts from Taylor High School and Veeresalingam Theistic High School. (Photo: S P K Gupta)

Entrance to the Ramakrishna Ashram in the 1920s. (Courtesy: Ramakrishna Mission)

The maya theory was just too loftily passive for his temper. He needed to react strongly to pain.

Possibly, this philosophical disagreement could have been confined to the cerebral level without affecting his medical leanings. After all, the Mission itself had more than one sphere of functioning. It functioned on the Vedantic level as much as on the Dvaitic level of social service. Likewise, couldn't he have tried for admission into the Mission for his spiritual growth despite his doctrinal differences with it, and served the people with his medical skill? He could have. But his mother's permission, that he needed to enter the Order, he was never going to get. Venkamma was firm in her refusal to give it to him.

So his medical studies went on, in the face of severe lack of money, and severe internal turbulence. And it was amidst these flounderings of his in the swamps of want, want of various kinds, that he strayed into marriage. He was hardly the eligible bachelor. He said so himself candidly, when his destined bride's father pressed him.

But he had his youth. He had his lineage and pure brahmanical genes and gotra. He had his education, had his assured future as a doctor in the making. Against these solid assets, even if they were as yet nascent, his lack of means receded into the shadows. It even lent him a touch of appealing pathos.

His destined wife's grandfather, Kastury Suryaprakasa Rao, was a prosperous farmer. At the railway station where he came to see him off, he pressed Rs. 120 into his hands. The money did double duty. It paid for his education, and at the same time forged the subtle bonds of obligation. 'You can pay it back at your convenience,' Suryaprakasa Rao beamed at his catch.

Like so many illustrious Indians before and after him, SubbaRow showed a fatalism and weak acquiescence about marriage. He didn't say no to Suryaprakasa Rao, even though marriage had never figured in his thinking. He didn't say yes either. But he could stay with good conscience in the no man's land between yes and no. He could play the part of the reluctant groom without being taught, from reflexes still alive in his dissenting self, and coming to surface under stress.

He gave himself options, in the time-honoured prerogatives allowed him. There would be no consummation of the marriage till three years after he got his degree, he said. And secondly, he would marry the younger girl, Seshagiri, the paternal cousin of the girl Suryaprakasa Rao was giving him. His demands were met. Chronology after all was a flexible factor, when a family had on its hands more than one girl of marriageable age.

Swamins of the Ramakrishna Mission, in the 1920s, who persuaded SubbaRow to become a doctor and serve the mission clinics when Venkamma declined the permission mandatory to enter their monastic order. (Photo: Ramakrishna Mission)

Victoria Hostel, Chennai: Amidst his spiritual quest, SubbaRow was forced to attend to his college lessons out of fear roommate B Narayanamurty would end financial support. (Photo: S P K Gupta)

The marriage would take place some six months later. But before and after it, much water was to flow down the river, giving form and shape to the man he was going to be.

Diarrhoea struck him. A vicious kind that drained him out and reduced him to a bag of bones of some 90 pounds. Allopathy did not cure him. Ayurveda proved to be the life-saver. Dr Achanta Lakshmi Pathi the Ayurvaid revived his rapidly falling pulse with a simple treatment of fresh juices. SubbaRow rallied round with the fourth or fifth dose. His weight went up to 138 pounds. Death was not imminent.

Dr Lakshmi Pathi diagnosed his case as tropical sprue. The disease was to cross his path twice again. Two of his brothers, Purushottam and Krishnamurti, fell prey to it.

Was there never to be any established cure for this disease that could kill at will?

More than twenty years later, in 1945, he was to find the cure in folic acid. But the first stirrings in that direction were precipitated now as he saw the bodies of his brothers, hollowed out by sprue, being consumed by the funeral fires.

The Ayurvedic system, and its practitioner Lakshmi Pathi, were also to play crucial even though short roles in his life. His own recovery by Ayurvedic medicines made a deep influence on him. The system could be fused with allopathy, he thought. According to the Tridosha Theory of Ayurveda, human health depends on the harmonious functioning of the three psychic cum physical divisions of the organism: the Kapha, the phlegm-based protoplasmic matrix, the Pitta, or the thermal mechanism within that determines the metabolic processes, and the Vata, or the psychic components which govern the nerves and the transmission of sense impressions, thoughts and emotional impulses.

Madras Presidency College, Chennai: After matriculation, SubbaRow enrolled in the intermediate course of the College, opting for Mathematics, Physics and Chemistry besides English and Telugu. He gained distinction in Mathematics and was encouraged by professors to take the honours course in mathematics but he applied for admission in the Madras Medical College. (Photo: S P K Gupta)

Madras Medical College. SubboRow did his bit for the freedom movement by wearing khadi surgical gowns and got failed in surgery by his British professor. He consequently got only the LMS certificate. Denied entry to medical service, he set to strengthen the medical armamentarium. (Courtesy: Prof. M Ganapathy, Chennai Medical College)

Couldn't this subtler approach to health and organic functioning be integrated with the emphatically physical approach of Western medicine?

Eventually, as things turned out, these comparative hypotheses of his got dropped on the way. Years later, the 'General Adaptation Syndrome' of Han Selye of the University of Montreal's Institute of Experimental Medicine and Surgery did bear him out by explaining pathogenesis in terms very similar to the Tridosha Theory.

But by then his own involvement with Ayurveda had cooled off. Many factors contributed towards it, many criss-crossings of circumstance. From within these his trail to the future was being beaten out unobtrusively and inexorably.

America was making overtures to him in vivid, futuristic gestures. Why America? Why not England? The question bears asking because England was more the land of destiny for ambitious Indians like himself. But colonial interactions could be estranging or attracting. In SubbaRow's case they were estranging. They incited rebelliousness. Gandhi was his reigning deity, not the King-Emperor. And Purushottam, his brother, further strengthened his anti-British leanings. He had been an active participant in the freedom movement and had suffered life-long in consequence.

Other incidents too impacted upon him, paving the road to America. There was the case, for instance, of the High Court lawyer, Sir S. Subramania Aiyar. He wrote to President Wilson after he read his forceful speech to the US Congress on the liberal creed, and the moral duty of the United States to go to war with Germany. Subramania Aiyar expressed the hope, in his letter to him, that he would convert England to his liberal sentiments. The British threatened to prosecute him for sedition. Subramania Aiyar replied by giving up his knighthood.

Then, there was his chance meeting with the Rockefeller grantee, John Fox Kendricks, a young American doctor. Yes, Kendricks assured SubbaRow, his medical degree from Madras Medical College would be recognised in American medical institutions.

SubbaRow had got his medical certificate some time before his meeting with Kendricks. He'd got an LMS, not a full-fledged MBBS, for he'd failed in the surgery paper.

Madras Medical College, Chennai: It challenged his metaphysical concepts; it revealed the inadequacies of Western medicine. (Courtesy: Prof. M Ganapathy, Chennai Medical College)

But he had impressed and even 'frightened' his classmates and teachers with his photographic memory. He could reproduce texts word for word, without effort. It earned him the label of a cheat at one examination, for his answer was the exact replica of that in the book. The teachers insisted on re-examining him. He repeated his performance. He couldn't help it, really. The teachers had to eat their words, had to recognise his special gift.

He was clear about what he wanted to do. He wanted to do research. He did not want to set up shop as doctor and go into practice. He applied to the Harvard School of Tropical Medicine for admission. He would take the Harvard University final examination if his Madras degree was found inadequate, he said.

He got admission without examination. But no travel grant was being given. He pinned his hopes on Purushottam persuading the Malladi

SubbaRow and Seshagiri in the studio portrait after the wedding: Mistress Science snatched him away. (Studio Photo courtesy: R R Kasturi, restored by Ramlal Lekhi)

Malladi Satyalinga Naicker Charities (Headquarters in Kakinada): SubbaRow went to Harvard with its scholarship. The terms of the scholarship were responsible for his initial biochemical studies and research. (Photo: S P K Gupta)

Satyalinga Naicker Charities to give him a scholarship. They had a programme of assistance for studies abroad once a year to a deserving student. SubbaRow hoped for their endorsement of his candidacy, through the good offices of Purushottam, who knew one of the trustees.

This was when Purushottam died, followed soon by Krishnamurti, the younger brother.

His scholarship prospects sank. He applied for a job in the provincial medical service of Madras. He didn't get it. Lakshmi Pathi, the Ayurvaid who'd cured him of sprue, offered him a job as lecturer in anatomy and physiology in his Madras Ayurvedic College.

He had no option but to accept it.

But the worst was yet to come. He'd compiled a 427-page manuscript on the vegetable drugs of North India as described by some of the giants of Ayurveda—Charaka, Drudhabala, Vrudha, Susruta and Vagbhata, both the elder and the younger. He wanted the book to be of use to all medical practitioners, whatever their school or system. Perhaps it was a grandiose idea. But what he woke to with chilling knowledge was that his employer Lakshmi Pathi was no more than a medical-politician, a run-of-the-mill medico,

The Madras Ayurvedic College is now a forgotten centre of experiment: shops have come up at its site. (Photo by S P K Gupta)

hardly the one to be driven by a thirst for knowledge and for opening up new frontiers in medical science.

This, more than anything else, gave him a feeling of dead-endedness. It made his poverty more painful. It made the seventy rupees a month he got as salary seem even more of a pittance.

For doing research one needed equipment, money, resources, he realised in a slow but sharp awakening of practical wisdom.

It would have to be America, he saw with fresh conviction.

He confided his fears and his desires in his wife, Seshagiri.

The closeness that developed between him and Seshagiri, who had just entered her teens, was

Farewell by the Madras Ayurvedic College: He advised the students to win acceptance for the theories of Ayurveda by modern physicians, and said he hoped to gain by his American studies a greater understanding of the relevance of its theories for modern medicine. (Photo: M S Pillay; courtesy: N Kesavacharlu)

probably among the real, even if fragile, blessings of this period of his life. She identified with him fully and unreservedly in the way an Indian wife so often can. And she identified not only with his hopes and aspirations, but also with the skimpy living which was all that he could give her.

Lakshmi Pathi raised his salary to a hundred rupees a month; Venkamma came over to help out her greenhorn daughter-in-law. A sister of Seshagiri also came as a peer cum morale booster. Added to this were the more than occasional visitors who are a feature of any Indian family, joint or extended. For this whole ménage the 100 rupees from Lakshmi Pathi was the mainstay.

He walked barefoot to his college every morning. The tram was an occasional luxury. He bought himself a bicycle, 'personal transport', from the fee he got for treating—under Lakshmi Pathi's pressure—an ailing zamindar. Often there was no shirt beneath his coat and his bare chest was freely visible to the students.

Couldn't they go to America together, Seshagiri asked him. SubbaRow had no answer for her. Guruswamy, the astrologer, had said that 'sea voyage' was not indicated in her horoscope.

But it was not astrological predictions that stopped him from a spontaneous 'yes' to her query. There were other reasons.

Kastury Surya Narayana Murty and Mrs Murty in 1965: Along with his father, Surya Narayana Murty helped SubbaRow complete his medical education, gave him his daughter in marriage and advanced funds against a prospective scholarship for getting started in his education at Harvard. The marriage failed but SubbaRow saved the Kastury family with his remittances when it was on the verge of collapse because of business losses and heavy debts.
(Photo: S P K Gupta)

Muthu Mudali Street (in 2000): Here SubbaRow set up family with Seshagiri in August 1922 only to wind it up in June 1923 to prepare for the journey to Harvard.
(Photo: S P K Gupta)

He'd managed admission once again in the Harvard School of Tropical Medicine. No research work would be allowed on his pet project of codifying Ayurvedic medicines, was the stern injunction of Dr. Richard Strong, Dean of the School; and secondly, there was to be no scholarship.

SubbaRow's problem was to muster the finances. And for this he became amoral, as he could, under stress: as perhaps any man can. He broke his vow against private practice of any sort by making hospital arrangements for the ailing wife of Dwarampudy Rami Reddy, a family friend. Reddy had political clout. The clout came in useful. A trustee of the MSN Charities sought Rami

Reddy's help for getting into the Madras Legislative Council. Reddy traded his support for the grant of the MSN scholarship to SubbaRow.

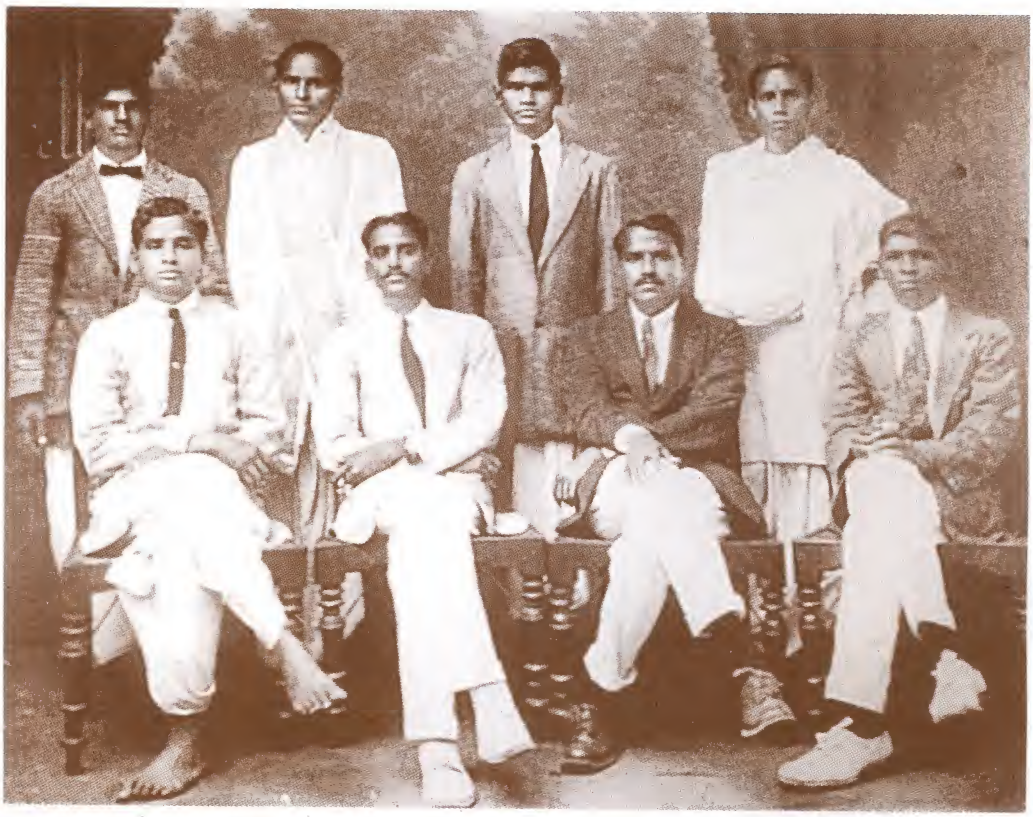
To all purposes now, money was assured. But it was late in forthcoming. And his date for embarking was nearing. His father-in-law came to his aid, and gave him Rs.2,500, for fare and immediate expenses of stay abroad.

The road was more or less clear now. The winding up operations of SubbaRow's modest establishment at Muthu Mudali Street were set in motion.

Seshagiri had no say in all this. Neither her age nor custom gave her a say. She had to content herself by giving an unwilling consent. She clung to his promise to return in three years. But the immediate prospect before her was daunting: a life of semi-solitude, amidst the probing eyes and wagging tongues of neighbours that her husband was a runaway by temperament. That he had deserted her.

She turned a deaf ear to gossip. But she couldn't shut down the noise and din of her own fears beating about within her that the gossip was not without truth.

Quietly, she prepared herself for the peripheral living laid down for a woman whose husband was alive, but away, ever away.



With students of Ayurveda. They were overawed by his felicity to refer them to specific passages in the textbooks not before him and he had a way of getting them easily understand human physiology. A disciplinarian in the classroom, he was quite informal in the house where he roomed with them for a while. Senior students made an earning by treating patients. SubbaRow declined private practise in the rooming house because of scruples about medical practice. (Photo by Carnatic Studio, Madras; courtesy: P Sitarama Rao)


SCIENCE · SIMPLY · PROLONGS · LIFE · RELIGION · DEEPENS IT

The Immigrant Scientist

S.S. Kashgar: She took SubbaRow to London on his voyage to America. He was lonesome among the eight Indian hopefuls setting out West; he was the lone vegetarian at the dining table where others feasted on 'ten different dishes of flesh every day'. (Picturecard courtesy: R R Kasturi)

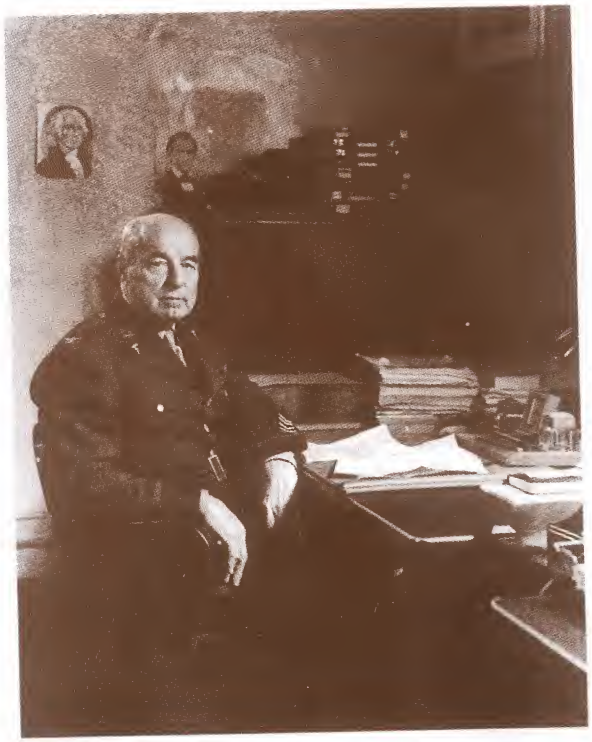
The odds were stacked heavy against him.

SubbaRow was in Boston on the Twenty-Sixth day of October 1923. It was night time, nine o'clock. The immediate problem was to find a place to spend the night. A rooming house for the down and out at 12 Havilland Street, Copley, offered shelter.

Lying on his back, staring up at the grimy ceiling of the mean bunkhouse, SubbaRow reviewed his position calmly. He listed the dues he had to clear. He had on hand one hundred dollars. After deducting the cost of room and board the hundred would dwindle. The tuition fee for registering at Dr Strong's Harvard School of Tropical Medicine was one hundred and fifty dollars.

How was he to make up the deficit?

He was not in panic. Nor was he reproachful of the fates, neither now, nor ever later. A child-like but sustaining faith in human goodness saw him through his crucial probationary years in America. Help came, as he'd had a gut feeling all along that it would. Dr Strong, the head of the HSTM lent him the money for registration and



Dr Richard Pearson Strong (1872-1948), Director, Harvard University School of Tropical Medicine: He did not encourage SubbaRow's ambition to work out the theories of Ayurveda and standardise herbs for all medical systems but enabled him to survive his first year in Boston by advancing term fees and adjusting courses to the hours SubbaRow had to keep at his subsistence jobs. (Harvard Medical Library, courtesy: Robert W Lovett)

for some immediate expenses. Not only this. Money came also from an anonymous donor, a young doctor doing graduate work.

His faith in human nature made him proof against the ethnic intolerance that marked the American temper of the 2Os. Boston was no longer the transatlantic outpost of the liberal outlook it had been in the seventeenth and eighteenth centuries. Even for Englishmen, as Dr J. C. Aub of the Massachusetts General Hospital put it, America was very American. And, difficult to 'establish normal relations with', as was further pointed out by Carl Rupert Addinall an Englishman who was in Harvard in 1924.

For SubbaRow, with his different colour and pigment, the going was doubly difficult. Although he had a degree from the Madras Medical College that was good enough for admission to the Harvard School of Tropical Medicine, it couldn't earn him an internship because the Massachusetts State Board of Medical Licensure wouldn't give him a licence on its basis.

Eventually he landed a job as night porter in Peter Bent Brigham Hospital at fifty dollars a month. He washed bed pans and urinals for three hours every night — either from eight to eleven or seven to ten, or from nine to midnight.

Dr Strong did all he could, pulled all the strings he knew, to stop the shameful spectacle of a qualified doctor doing scavenging work. He wrote to a colleague in the Boston City Hospital for a lab assistant's job for SubbaRow. The colleague conferred with another colleague, but nothing gave. No funds in the kitty, was the stock reply.

Dr Strong was not fobbing him off. Far from it. The School of Tropical Medicine was in genuine financial difficulties all through Strong's years. For

Boston YMCA (in 1965): SubbaRow stayed here for a while before moving to the dark basement room at Wigglesworth Street. (Photo: S P K Gupta)

23 Wigglesworth Street (in 1965), Boston, in whose basement SubbaRow lived (1923-24) while student of Harvard School of Tropical Medicine.
(Photo: S P K Gupta)

some time it operated simultaneously from the Harvard Medical School and the Harvard Public Health School. A few years before SubbaRow joined, it was made administratively part of the latter. And when Strong retired it was amalgamated with the Harvard Medical School's Department of Comparative Pathology. In short, it had a chequered existence, affecting its financial resilience as well as Strong's capacity to help SubbaRow. He stood by the young, immigrant scientist, nonetheless. He it was who worried that the night work in Brigham Hospital would affect his health, and hence his studies. So, when his efforts to get him a lab assistant's post in Boston City Hospital's Department of Tropical Medicine– either from seven to ten in the morning or five to eight in the evening— did not bear fruit, he did the next best thing he could: re-arrange SubbaRow's lecture attendances to help ease the strain.

SubbaRow did not lack well wishers even in his worst days. The combination of intellect and lack of means that he had, compounded by his foreign appearance, stirred the nobler, giving sentiments of many. Even when lack of means went and was no more a factor, the charisma remained, impelling many to go against established rules for his sake.

And so SubbaRow pursued his courses of study in Harvard School of Tropical Medicine side by side with his job as ward cleaning boy — a human vacuum cleaner, in effect — in Brigham Hospital. It saw him through his first year in Boston. He slept in the dark basement of 23 Wigglesworth street from midnight, when his scavenging duties ended, till 9 a.m., when his classes began. He had no clothes other than those he'd brought from India. For food he could just about afford shredded wheat and milk. Later on, when even that went beyond his means, he settled for beans.

Of the subjects in the School of Tropical Medicine, parasitology interested him the most. Dr Strong was partly responsible for this bias, for he exempted him from courses like dermatology and hygiene, which he'd already done in the Madras Medical College, and encouraged him to specialise in parasitology.

It proved invaluable training for the research in filariasis and trypanosomiasis (sleeping sickness) that he initiated years later. And it was in these fledgling years too that he was initiated into the methodology of research. He learnt it in the course of a four-month stint with Dr Ernest E. Tyzzer on the cultivation of *Entamoeba coli*, a non-pathogenic protozoan parasite that infests the human intestinal tract.

'I am learning how to do research, how to proceed,' he wrote home. Finally on June 1, 1924, less than a year after his enrolment — eight months, to be exact — he got his Diploma in Tropical Medicine.

Two months earlier, in April 1924, he had got news from his father-in-law of the birth of a boy to Seshagiri and him. It didn't make him elated. It made him fatalistic and prescient in the way his Indian samskaras always could at climactic

Peter Bent Brigham Hospital (in 1965) : A fully qualified medical doctor, SubbaRow was its most distinguished night porter, doing a menial job of washing patients' bedpans and urinals that provided a monthly wage of $50 to cover his basement room rent and provide something to eat while on duty. He nevertheless gave it a good chit by writing home of his high esteem for its two chiefs of clinical service: neurosurgeon Harvey Cushing and heart specialist Henry Christian. (Photo: S P K Gupta)

points of his family life. Predictions and soothsayings that had been made about the birth backwashed into his mind as if on cue. The child was doomed to die in less than a year after birth, he wrote to his father-in-law in chilling, blunt words. The astrologer had told him so. Seshagiri herself would afterwards be critically, but not fatally, ill. The main thing, he said, was to make her get used to the idea of the child's impending death so that she was prepared when it happened.

Seshagiri roused his concern more than the child. She became the urgent, sought presence for him, not the child. Give the child any name you wish, he wrote back, when she asked him what name he would like given to his son. He was as much hers as his, he said. Such a just and sober attitude from him alarmed Seshagiri's people. They wanted effusiveness, joy overflowing, a son-in-law raring to rush back home and feast his eyes on his child. Why was he so unmoved, they asked him.

A child was no gift of the gods, he replied. It was just an accident, a fall out of hungers that seize a man and woman. He would meet all his obligations to his child, but he would not sing at its birth, nor weep at its death, he said.

The child lived till December — some nine months or so — almost the length of time outside its mother's womb as inside. It died of a red rash that first appeared on the thigh and then spread rapidly. Death occurred ten days after the outbreak of the rash.

He diagnosed the rash as erysipelas, a streptococcal infection. Neither Western nor Ayurvedic doctors could have saved the child, he

said. The only remedy was serum therapy, he said. And he told his father-in-law to make a note of it for future use. 'An enterprising doctor can inoculate the tube I have sent to the King's Institute, Guindy (Madras) and prepare the vaccine. This is guidance for the future.'

He was not really as unmoved about children and the event of birth as he said he was. His career, in the years that followed, was dotted with special relationships he built up with the children of his colleagues. But the pressure of work made him brusque. The claims of family and kinsmen that were being made on him with a sense of prior right he rejected instinctively as arbitrary and presumptuous. They threatened to usurp his time with himself and his work. But amidst these rejections, he was also upholding his bonds with Seshagiri. He was upholding the solemnity that marks a man taking a woman as wife. He was, in short, upholding values.

A greater warmth and closeness grew between him and Seshagiri. He consulted her on his duty of repaying her father the travel loan he had taken from him. They made plans for living together, for picking up threads again. Nothing came of these plans. But that they were made, that something like a bilateral relationship was growing between them, are facts that should not be overlooked.

Professor Otto Folin (1867-1934), Head of HMS Department of Biochemistry: He assigned SubbaRow the working out of the phosphorus method, encouraged his muscle chemistry research, secured him a Rockefeller Fellowship, had him often at his home for dinner but could not, in the racist milieu of Harvard of the times, get SubbaRow his due position in the faculty. Conscious that Folin was doing all he possibly could for him, SubbaRow virtually worshipped him and said of his mentor: "Everything I am here at Harvard I owe to him." He was deeply distressed when Folin died. When he made the condolence call, Mrs Folin told him: "My husband regarded you as the most brilliant and promising of the Department and was sure you would go far in research if given opportunity." (Photo: Harvard Medical Library, courtesy: Robert W Lovett)

Harvard Medical School (Biochemistry Building to the right): Harvard was SubbaRow's foster mother ('alma mater'); it trained and sheltered him for over a decade but failed to appreciate his contribution to biochemistry that lay in his discovery of phosphocreatine and ATP which provide the biochemical energy for muscular contraction and which get the world's work done. It also failed to provide a place for his life's work: the conquest of disease. (Photo: S P K Gupta)

His trials, any way, were far from over yet. In fact they seemed to get a fresh lease of life. He lost his fifty-dollar job at Brigham Hospital. The reason: over staffing. Some monetary help came with the release of a part of the first year's grant from the MSN Charities in India, his financiers. Under the terms of the scholarship he was not to use the money for any course in general medicine.

He therefore enrolled in a summer course in the Department of Biochemistry at Harvard Medical School.

The grant took care of the fee for the course. But what about money for food and housing? Dr Strong was away in South America. The MSN Charities did not respond to his request for an advance from the second year's scholarship.

Once again his trust in human goodness came in for vindication.

A Mr Watson of New York City sent him thirty dollars a month for the summer season. SubbaRow might not have survived that summer in Boston if this had not happened.

Luck turned now. His supervisor in the Department of Biochemistry was Dr Cyrus Hartwell Fiske, a brilliant ex-student of Professor Otto Folin, the head of the Department. Fiske and SubbaRow established a good working relationship almost straight away. And midway through the first research assignment set by Folin to SubbaRow, Folin ended his probation, took him in as a regular graduate student and got him a library assistant's job. Simultaneously he persuaded the Faculty of Medicine to give SubbaRow a scholarship. And capping all this came the increase of the MSN Charities scholarship money from Rs.1000 to Rs.2000.

The tide had turned, definitely.

He still had to live cheap. But he did not have to live dirt cheap, down and out. Nor did he have to lean on the crutches of donations from unknown donors, however kindly and well-meaning. He could indulge himself in small ways. With the first instalment of the medical faculty scholarship, he bought himself a second-hand microscope up for sale on the death of its professor-owner. The school fee for which the scholarship was intended remained unpaid till the MSN Charities sent in the second remittance.

But these were the occasional flings of a man naturally spartan in his way of living. Thrift was a part of his value system. His room rent was Rs. 40 a month, among the cheapest in town. His food expenditure was Rs.3 a day. "I can get on even if I get not a pie from India," he told his people. Bare-bone living suited him to the t. Coupled with his work in the lab from eight a.m. to well past midnight with short breaks for refreshment, which kept him at his creative best, he was living life to the hilt. 'My health is perfect', he wrote home. "I weigh five pounds more than I did in Anaparthi."

Cyrus Hartwell Fiske (1890-1978): Supervised SubbaRow's work on the Phosphorus Method and collaborated in the discovery of Phosphocreatine and ATP: He set the task, gave guidance but left SubbaRow mostly on his own and wrote up and presented the 'joint' work. Harvard colleagues say SubbaRow's contribution rose incrementally and Fiske's became increasingly minimal as the collaboration progressed. A change in Fiske's personality locked up the post-ATP isolation of phosphorus compounds including two nucleotides arguably involved in the synthesis of RNA. When Fiske's promotion as Head of Departments was in jeopardy, SubbaRow gave all the credit to Fiske and minimised own role. The loyal sacrifice did not get Fiske his promotion but jeopardised SubbaRow's own career and hampered his vitamin research at Harvard. (Photo: Harvard Medical Library; courtesy: Robert W Lovett)

It created a stir, not just in biochemical circles, but in all of Harvard Medical School. SubbaRow became something of a legend, fostered unwittingly by his presence and appearance. His colour distinguished him straightaway, for one thing. He wore a long white oversized coat that flapped around him as he made his way down corridors and into rooms. He had a shuffling gait. There was a slight stoop to his shoulders. A half lit cigarette was ever present in one corner of his mouth. Medical students stared at him with awe as he went past.

But he wasn't the unapproachable, ghostly figure he seemed. All he needed was the right person to draw him out, somebody in whose company he could let his guard down, free of inhibition.

Perhaps it was a two-way process. Perhaps the students wanted his company too, wanted the excitement and cut and thrust of a different mind, a different culture, crowned by achievement and intellect. Charles Henry Finke was certainly one who did want it. Finke made several false starts. SubbaRow just wouldn't oblige. Finally, Finke took the bull by the horns. He wished to speak to him, he told him straight.

SubbaRow shifted his cigarette to the other corner of his mouth.

"Come to my lab. In the afternoon', he grinned.

The lab was littered with scratch sheets, up to its ears with glass works and other tools of the trade.

SubbaRow finished his job on hand.

"Good morning!" It was late afternoon. He was not grinning, but he showed no more than a hint of the growls. Well, what did he want?

His name was Charles Henry Finke, Finke began. He'd called because they were neighbours. Neighbours should be friends, he thought ...

Silence.

"You are a good boy," said SubbaRow.

He was? But he was a confused boy at the moment!

Why so?

He was daunted by all the equipment that Dr Cyrus Fiske had installed in his lab, Finke went into a lament.

Take a day or two off, SubbaRow advised the youth. Problems had a way of disappearing with time.

Three weeks later Finke came up with a genuine problem, immediate and pressing. He needed a barrel of pig's blood. For fractionation. Fiske's orders. Where did one get the stuff?

SubbaRow phoned his favourite slaughterhouse in Charlestown. Get your car, he told Finke.

They loaded the barrel of blood in their car. On their way back a policeman stopped them. What was that fluid leaking from the back of the car?

The barrel had sprung a leak. A pool of blood gleamed darkly on the road.

Finke explained the blood. He showed the policeman the receipt from the slaughterhouse.

They were allowed to go. But all SubbaRow's fears of the coloured man in an un-coloured society rose up, stark, for a minute. The policeman might accuse him of murder simply because of the colour of his skin. He could be deported for some minor violation of traffic law. Below his cool exterior he was shaken. And his ever present, secret dread of unjust and instant deportation was communicated to Finke as a fully understandable human condition without the odium of personal shortcoming attaching to it. Their association had struck the right chord of respect and informality

Their good times together increased. A third member, Carl Addinall, an English ex-soldier of the British Army in India, presently come to Harvard, joined them. Finke and Addinall were tennis buffs, lithe, swift-footed and at ease with their bodies in a way SubbaRow had never learnt to be. He was just a shade too cerebral, his body a shade too reined in by his mind. It was a shortcoming never overcome by him. All the forays he made into activities such as driving and flying, demanding quick physical reflexes, confirmed it. He took his lack of prowess in stride. There were spheres where he had prowess and more. Nature had her own way of making up for shortfalls here with surfeit elsewhere. He was undisputed leader in the laboratory. His conquerors on the tennis court acknowledged his sway in the lab. They spent much time there with him, and often, if they were still around after six, they took him out to dinner.

He was beginning to see himself mirrored in others' eyes. He was beginning to like what he saw. And he communicated this pleasing self-image to Seshagiri, in the cautiously boastful tones of the man coming clear of his reserve.

The process, actually, had started back in 1924-25, the year of the Fiske-SubbaRow Method of estimating phosphorus. The first whiffs of ease and a life more roomy had already come with an invitation to dinner from Folin, the head of the Department, at his house on 133 Buckminster Road. Folin was congratulatory. And he was also celebrative of the invitation to his protégé from the American Society of Biological Chemists for a demonstration of his Method. He would get him a bigger fellowship next year, he toasted his student.

And SubbaRow reported it all to Seshagiri. If the Congress of the American Society of Biological Chemists approved the Method, all the medical schools in the US would adopt it, he said. And when his paper was published he would send a copy to her. And he hoped she could see that he wasn't exactly wasting his time. He wasn't idle for even an hour, he said. "But please do not advertise," he became cautious, confidential. "Publicity is bad. I beg of you not to talk of this to anybody."

Seshagiri and her people prayed for the success of the demonstration. If SubbaRow was emerging into a fuller life, she too was moving into fuller womanhood. A teenager yet, she was pregnant with their first child.

Two personalities were unfolding, two personalities in different circumstances, of different temperaments.

From his first assignment he won a recognition that has stood the test of time. There was a prologue to this task set for him by Otto Folin. It lay in the establishment of a clinical procedure called Colorimetry. Professor Folin was the founder of this procedure. By it, blood, urine or tissue could be analysed on the basis of their colour intensity when they were dissolved with the help of reagents. Folin had used this method for determining the creatine and creatinine content of tissues. For determining the phosphorus content of tissues, two of Folin's associates converted tissue phosphorus to phosphomolybdic acid and, with the help of hydroquinone, broke this product into a blue substance. This substance could be subjected to colorimetry. But there was a snag. The substance faded too quickly. To remedy this, another associate made certain modifications but that increased the reaction

time. And that brought about its own complications. Other substances in the tissue interfered with the reaction. This reduced the colour intensity by one fifth the maximum possible. And most important of all, it increased the margin of error to ten per cent from four.

SubbaRow's task was to find an alternative reagent to hydroquinone that would completely break down the phosphomolybdic acid in a short period. There were three 'should nots' to be kept in mind in this quest for a new reagent. One, it should not be affected by other tissue substances that are activated in the reaction. Two, it was to be proof against trichloroacetic acid used to remove protein matter from tissue meant for analysis. And thirdly, it should not need sulphuric acid to digest the phosphorus. For, in large quantities sulphuric acid retards colour intensity, and in small quantities makes for phosphate loss.

The first step forward came when a reagent called 5-aminosaligenin was found to have a breakdown time of thirty minutes and colour intensity twenty per cent more than hydroquinone. But Folin wanted a reagent that took no more than five minutes for the breakdown along with maximum colour.

With this stipulation, the second phase of experiments started and yielded 1, 2, 6-amino-naphthol-sulphonic acid, fifty times more active than hydroquinone, taking a fraction of a minute for the colour intensity that hydroquinone took thirty minutes to produce.

This was very encouraging, of course. But 1, 2, 6-amino-naphthol-sulphonic acid was difficult to prepare. However, an isomer, 1, 2, 4-ANS acid was equally good. Not only could it be prepared easily in the laboratory but it was also available in the market under the name of 1, 2, 4-acid, used by dye manufacturers. For the next four months, it was work round the clock to perfect the method and establish that it could withstand the salts in tissues. It was work that "took at times my life out", he recalled later. No changes in the procedure for preparing analytical material for colorimetric readings was required. The phosphorus, as before, was converted into phosphomolybdic acid with the help of the regular molybdate concentration (2.5 per cent of ammonium molybdate in 5N sulphuric acid). To this solution was added the 1, 2, 4-acid to get the blue colour for colorimetry. The molybdate concentration was suitable not only for preparing the colorimetric standard but in urinalysis. SubbaRow worked out the concentrations suitable for inorganic phosphate analysis of blood filtrates and for total phosphate analysis of blood and tissues. It was "correct to 1/100,000th of a grain", SubbaRow recorded.

A public demonstration of the Method was given at the Annual meeting of the American Society of Biological Chemists on December 29, 1924. The demonstration was an unqualified success. A 26-page paper by Fiske and SubbaRow detailing the Method was published in the *Journal of Biological Chemistry* in the December 1925 issue. The Fiske-SubbaRow Method for analysis of clinical and biological material is in use to this day in carbohydrate metabolism, lipid metabolism and muscle chemistry.

Moreover, the Method has become an important tool for diagnosis of metabolic diseases. For high phosphorus levels in blood plasma may lead to kidney failure, metabolic acidosis, cretinism and goitre. And low phosphorus levels, on the other hand, are seen in rickets and osteomalacia (softening of bones). Hence measuring phosphorus in body fluids is almost the first procedure a biochemistry student learns. And the choice of generations of biochemists and pathologists has been the Fiske-SubbaRow Method.

Recent observations of the link between phosphorus balance and prostate cancer has opened up the possibility of the Method becoming even more important as a screening tool.


SCIENCE · SIMPLY · PROLONGS · LIFE · RELIGION · DEEPENS · IT
YELLAPRAGADA SUBBAROW
1896–1948
SCIENTIST · TEACHER
PHILOSOPHER
HUMANITARIAN
DIRECTOR OF RESEARCH
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY

A Whiff of Fame

HMS Biochemistry Department, 1932: Fiske, Folin and Trimble are second, third and fifth in the front row; the first two in the middle row are storekeeper Martin, colleague with whom SubbaRow (second on the top row) would have his weekday lunch of sandwiches, seated behind packing cases; and last on the top-row is charwoman Tracy, a person with a wonderfully earthy sense of humour and special fondness for SubbaRow, who was saddened when his teasing prediction came true that she would die of a heart attack if she did not stop eating and working so hard keeping the laboratories clean. (Photo Courtesy: I S Danielson)

The method brought a mutation to his name, giving it a piquant Slavic flavour. So far he had written his name in the standard way—Subba Row. But the printer's devil intervened to combine the two words and make it SubbaRow in the *Journal of Biological Chemistry* issue carrying his joint paper with Fiske on the Method. Fiske did not correct the mistake. Puckishly, he had the R capitalised, and let the hybrid word SubbaRow be. For generations of biochemistry students he remained a Slav scientist.

It hardly bothered him. Nationality had no meaning for him, as he made clear in his behaviour with visitors from India. Not that mistakes of nationality always left him indifferent. In the America of the 20s, the coloureds were just 'them darkies' for the whites in a peremptory and humiliating erasure of racial distinctions that could hurt individual pride. Often, far too often, he was mistaken for an African. And always it left him chafing. It is difficult to reconcile the two attitudes of sporting acquiescence on the one hand, and hostile questioning on the other. Perhaps he saw the first as a bestowal of identity, and hence a gesture of friendship, however clumsy. The

second was a denial of identity, a contemptuous flattening to generic levels that could hurt the most indifferent man.

However that may be, the fact to bear in mind is that he was too immersed in work to make an issue of misspellings of name, or misreading of face. With Fiske he was embarking on new and exciting areas of research.

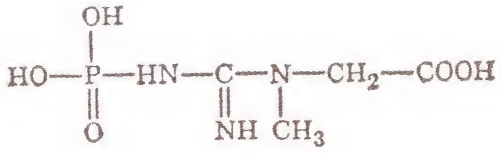
Their first discovery was Phosphocreatine, a compound of phosphoric acid and creatine. Scientists had long known that creatine was a component of muscle, but did not know its function. SubbaRow and Fiske came upon creatine while they were testing muscle for its phosphorus content. How they came to be doing this is a story in itself, a story behind the story, and illustrates the role of chance in scientific discoveries.

The parent story had its beginning in the long standing curiosity in the scientific world about the nature of muscular contraction. What makes the muscle contract, thereby fighting the force of degeneration and death latent in living organisms?

In 1907 two Cambridge researchers said that lactic acid was the motor behind muscular contraction. Shortly afterwards, the German biochemist Otto Meyerhoff proved that lactic acid was a breakdown product of glycogen, a starch present all over the body, especially in the kidneys, liver and muscle.

Next, Professor Archibald V. Hill of University College, London, proved that the heat produced during muscular contraction could be partly accounted for by the conversion of glycogen to lactic acid. For this theory, Meyerhoff and Hill won the Nobel Prize for Physiology and Medicine in 1922.

The question now was how was glycogen converted to lactic acid? A hypothesis was presented by G. Embden. He said that blood sugar and phosphorus combined to form an ester or a



Phosphocreatine (Source: Merck Index)

compound that breaks down glycogen in the muscle to lactic acid. This compound was hexose phosphate or sugar phosphate.

This was where SubbaRow and Fiske came in. They were conducting research on the effect of insulin on blood sugar. They postulated that if Embden was right, insulin should increase the quantity of hexose phosphate in the livers and muscles of diabetics. This was not borne out by their researches on muscle. Embden was wrong, they said. But they were wrong, not Embden. Insulin does increase sugar phosphates in diabetic animals, but since these are converted into lactic acid by enzymes working very fast, they could not be detected by the analytical methods then available.

Convinced (wrongly) that Embden was wrong, that the Embden-Hill-Meyerhoff trio behind the theory that glycogen and its breakdown product lactic acid were the forces that caused muscular contractions were totally wrong, SubbaRow and Fiske began on their study of the phosphorus compounds of muscle.

SubbaRow prepared the muscle filtrate for the study from cats. To obtain the filtrate he removed the muscle masses of stray cats he caught from the alleys round Harvard Medical School. The cat-hunting was unavoidable. Fund allocations from the Department were low. He had to resort to this method for the inputs he needed for the laboratory tests.

First, he anaesthetised the cat with amytal. Then he detached the muscle mass. Next, he dropped it into liquid air. This froze the mass.

A Tribute by Harvard

The discovery of Phosphocreatine in 1927 and of Adenosine Triphosphate (ATP)in 1929—body chemicals so crucial to the processes of life—by Cyrus H. Fiske, Assistant Professor of Biochemistry, and Yellapragada SubbaRow, his brilliant graduate student and able co-worker, were made on the Quadrangle at the Harvard Medical School. What a departure they were from the concepts predominating then! Fiske and SubbaRow possessed the enthusiasm, the fresh minds, and the skill to change the direction of biochemistry drastically, and within a span of five years, to bring it into truly fertile areas. First, they developed a sturdy and reliable method for phosphate determination—the cornerstone of their experiments and a method employed with only modest variations in hundreds of laboratories, world-wide, to this day. Using this excellent method, they recorded independently and with the greatest precision the release of inorganic phosphate during a muscular contraction and delivered the verdict that the highly labile phosphate compound in muscle was creatine phosphate!

Their elegant documentation and demonstration immediately sparked a chain reaction in the laboratory of the highly competitive Otto Meyerhof group at the Kaiser Wilhelm Institute in Berlin, then considered the intellectual centre for the study of the physiology and biochemistry of muscle function. The (rival) group confirmed the Fiske-SubbaRow discovery and pursued it in a multitude of ways.

Beyond any doubt, Fiske and SubbaRow fully realised the several implications of their own discovery of phosphocreatine, and the potentialities of a phosphorylnitrogen linkage. In a great classical paper, they formulated with the greatest care both the physicochemical and the physiological properties of phosphocreatine. Thus, the year 1927 marks the beginning of the era of high energy phosphate compounds, in biology.

The crucial role of phosphocreatine in the energy metabolism of muscle contraction was revealed early in 1930 by Einar Lundsgaard at the University of Copenhagen. It took the combined skill and wit of Fiske(-SubbaRow) and Lundsgaard to emancipate us from the lactic acid dogma of Meyerhof and A.V. Hill in muscle physiology.

In early 1929 Fiske and SubbaRow, using their mastery in the handling and the crystallisation of metal salts of phosphorus compounds, obtained a pure sparingly soluble crystalline silver salt of an adenylic acid derivative which they by their own careful elementary analyses identified as adenosine triphophate, ATP—perhaps the most important of all biological phosphorus compounds.

Karl Lohmann, whose mentor was Meyerhof, suspected in 1929 that the pyrophosphate he had found in muscle might be an artefact. He reported this at the International Congress of Physiology in Boston on August 29. In 1934, Lohmann discovered the enzyme that catalyses the exchange of phosphate between ATP and creatine, generating phosphocreatine and adenosine diphosphate, ADP. This was the first demonstration of the biological role of ATP, and one that established the interrelationship between the two substances whose chemical structure Fiske (and SubbaRow) had determined. In 1934-35, SubbaRow and Fiske concentrated their interest on the antipernicious anaemia factor of liver. SubbaRow now took the lead and, after his move to Lederle Laboratories, contributed heavily to the B-vitamin field.

Adapted from the Fiske Memorial Minute of the
Harvard Faculty of Medicine — Harvard Gazette, October 17, 1979

Then he pounded the frozen mass in an iron mortar, adding liquid air at intervals to keep it frozen. Then he mixed the muscle pulp with ice-cold trichloroacetic acid, and stirred it thoroughly. The protein in the muscle settled down, after which he poured out the fluid in a flask. Two hours later he filtered this solution. He neutralised it with sodium hydroxide. Finally he subjected the solution to colorimetry, his and Fiske's celebrated method for phosphorus estimation.

This was when things began to happen.

The solution did not turn a full, stable blue in four minutes as it was meant to. The colour kept on rising for thirty minutes. What was this due to? He and Fiske discussed the question. It did not seem to be due to a retarding substance in the muscle. If it were so, larger amounts of the sample would lead to a proportionately longer time in colour formation. In this case, however, the delay remained constant at thirty minutes whether the sample tested was 5 c.c or 10 c.c.

It could only mean that an organic compound was present in the muscle, which released phosphorus as the reaction in the colorimeter proceeded. This was indeed so, as they found out. The job now was to isolate this compound made of phosphoric acid and the other, unknown substance which affected the colour.

The isolation and identification work took a whole year. Two assistants of Hill, who also encountered slow colour formation from their muscle filtrate sample, now poured scorn on the Fiske-SubbaRow Method of Phosphorus Estimation. They said that it was inapplicable to muscle phosphorus. SubbaRow and Fiske replied that the British biochemists had missed the organic phosphorus compound because they had put their muscle filtrate in an acid solution which rapidly hydrolysed it, whereas they (Fiske and SubbaRow) had used sodium hydroxide and unravelled it.

Their analysis finally established the colour retarding element as a compound of phosphoric acid and creatine.

They called it phosphocreatine and presented a full picture of its range and action.

Phosphocreatine accounts for two thirds of phosphorus in the muscle at rest. When the muscle is stimulated the phosphocreatine level goes down and the inorganic phosphorus level goes up. Phosphocreatine disappears totally when the muscle is activated to the point of exhaustion. And then, when it is allowed rest, it re-appears.

It was a landmark in the history of muscle biochemistry. The force that governed muscular contraction was neither glycogen nor lactic acid, but this compound of creatine whose presence in muscle had long been a puzzle to biochemists.

In April 1927, phosphocreatine was formally announced in Rochester, New York, at the Society of Biological Chemists. On the 22nd of that month, SubbaRow and Fiske published a detailed paper on the compound in *Science* the journal of the American Association for the Advancement of Science.


SCIENCE SIMPLY PROLONGS LIFE RELIGION DEEPENS IT

Plunging Into The American Way Of Life

Vanderbilt Hall. Harvard students' hostel where SubbaRow shared a fourth-floor suite of rooms with fellow students when a Rockefeller Fellowship made it affordable. (Photo: S P K Gupta)

Visiting friends Joseph Fazekas and Harold Himwich at Yale. SubbaRow smokes and has a chocolate drink, both risk factors that contributed to his untimely death. (Photo courtesy: Harold Himwich)

The launch of Phosphocreatine in a bare sixteen-month period after the Phosphorus Method brought about marked changes in SubbaRow's life and life-style. Not that he converted to conspicuous consumption. But he didn't have to count every cent now. A Rockefeller Fellowship was in the offing. While it was pending Folin got his Harvard Fellowship renewed. When the Rockefeller materialised SubbaRow's income went up to 3300 dollars a year, a princely amount indeed compared to the fifty dollar and less a month he had been making till then as night ward boy in Brigham Hospital, and as night library assistant in the Harvard Medical School Library. He moved to a shared suite of rooms at the newly opened Vanderbilt Hall. For a while before this he roomed with two other assistants of Fiske at 80 dollars per head per month. This was a little on the high side, for the Rockefeller Fellowship was not yet in hand. And the social life was also a little too fast for his tastes. But SubbaRow was beginning to emerge from his cocoon. A spirit of sheer *joie de vivre* swept over him. He plunged into the American Way of Life with all the involved and yet detached curiosity of the sensitive outsider.

Harvard Medical boys on a deep-sea fishing trip at South Boston Harbour-side (Spring of 1926): back from Minot's Light after a sail during which they had fun watching sea-sick blue Sub, who recovered to catch the largest fish of them all and won the 'pot'. (Photo from YSR's Album, courtesy: R R Kasturi)

There was a postscript to the discovery of phosphocreatine. It was not a very happy one. The orthodox sections of biochemistry did not take kindly to the Fiske-SubbaRow discovery. They would not easily write off the Nobel Award winning theory of Meyerhoff and Hill, that glycogen and lactic acid were the motors of muscular contraction. They did everything they could to debunk phosphocreatine.

Among the conspicuous debunkers were Dr Philip Eggleton, a research fellow in Dr. Hill's Department, and his wife Grace Palmer Eggleton. They claimed that they had isolated an organic phosphorus compound which had strong bearings on the nature of muscular contraction. They thought this compound was the hexose phosphate that Embden had put forward in his hypothesis (in the early twenties) as the reacting agent that converted glycogen into lactic acid. They were not however fully sure of this. Actually it was phosphocreatine that they had stumbled upon while estimating the phosphorus content of a fatigued muscle. But their blind loyalty to Meyerhoff and Hill prevented them from seeing it. Anyway, they published their finding which 'confirmed' Meyerhoff and Hill, in *Nature* the British science journal, two months before Fiske and SubbaRow unveiled phosphocreatine at the Rochester meeting of biochemists, and again, in the March 10, 1927 issue of *Biochemical Journal*. Before they sent a third paper re-iterating their findings to the *Journal of Physiology*, in the issue that was slated for publication on July 7, Professor Hill drew their attention to the Fiske-SubbaRow paper on phosphocreatine at Rochester in April. The Eggletons re-examined their material and found creatine in it. But all they could or would say in the fourth paper they wrote, published on May 27 in *Chemistry and Industry* was, that creatine was associated with the compound they had discovered, and that creatine 'has a part to play in the chemical phenomenon accompanying muscular contraction'.

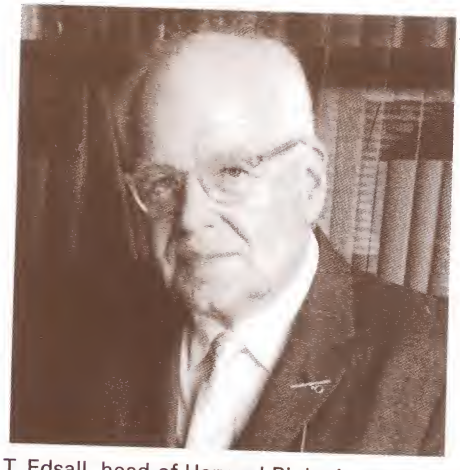
By February 10, 1928, however, Fiske and SubbaRow had got their additional data ready, and

With two of the Boston Harbour group (Photo from YSR's Album, courtesy: R R Kasturi)

Sparr's Drug Store (in 1965): An affordable eating joint during the penurious Boston years. (Photo: S P K Gupta)

systematically demolished the objections to phosphocreatine raised by the debunkers. In their second paper, published in the March 1929 issue of the *Journal of Biological Chemistry*, they boldly declared that 'some readjustment will now be required' in the views on the mechanism of muscular contraction that prevailed before the discovery of phosphocreatine.

Their paper was a 'landmark in biochemistry'.



John T. Edsall, head of Harvard Biological Laboratories, hails ATP as one of the real great discoveries, and gives credence to Fiske's belief that Meyerhof speeded up Lohmann's announcement to gain credit after learning on a Harvard visit that Fiske and SubbaRow were near an answer to the muscle energy puzzle.
(Photo: S P K Gupta)

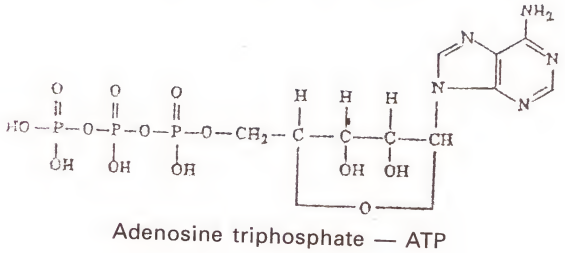
The Meyerhoff-Hill theory was repudiated in 1930.

But rumblings of dissent continued. The Eggletons and Professor Hill couldn't reconcile themselves to the demolition of their pet theory. But Meyerhoff was objective. He saw the importance of phosphocreatine and plunged into follow up studies in open competition with Fiske and SubbaRow.

Fiske and SubbaRow had a strong lead to work on. It went back to 1927, to the time of the unveiling of phosphocreatine. An unidentified compound had been obtained in muscle as phosphocreatine was dissociated. This nameless compound combined with the phosphorus produced during the dissociation process to produce a substance. What was this substance? And what was the nameless compound? SubbaRow speculated that the compound was either glyceraldehyde or dihydroxyacetone. To the substance that formed when it combined with phosphorous he gave the lengthier name Triose Phosphoric ester.

The finer points of the new substance became clearer by and by. As Fiske and SubbaRow were refining their process for making crystalline phosphocreatine and as they added an alkaline solution of calcium chloride to the muscle filtrate to remove inorganic phosphates, a calcium derivative came down in the precipitate. How had this happened? Why hadn't this calcium salt remained dissolved in the filtrate?

After they were fully through with the phosphocreatine work, SubbaRow and Fiske set to work analysing this salt. They found that it was



Adenosine triphosphate — ATP

a chemical in which adenylic acid was linked to two extra molecules of phosphoric acid. They called it Adenosine Triphosphoric ester (ATP). But it was about a year before they could publicly present it, thanks to Fiske's finicky attention to detail and crossing the t's and dotting the i's. Eventually in August 1929, at the 13th International Physiological Congress hosted by Harvard Medical School, at the fag end of the proceedings, SubbaRow performed the formal presentation.

There is no official record of it, for it was a last-minute, hence 'unofficial' presentation. Nor were the abstracts of the Congress papers, where it could have found a mention, ever printed. The only record of it is in a letter SubbaRow wrote home immediately after the presentation.

But the news really hard to digest was the item in the August issue of the German journal *Die Naturwissenschaften*. In the issue pre-dating the Physiological Congress by 16 days, Karl Lohmann of Meyerhoff's laboratory had written that he had isolated Adenosine Triphosphate! Lohmann, consequently, got the credit for ATP.

The fruits of victory for Fiske and SubbaRow, had, indeed, slipped between the cup and the lip. Fiske frankly suspected Meyerhoff of unfair means. Meyerhoff had come to the Harvard Medical School and to Fiske and SubbaRow's lab. Seeing the neck and neck it was between his and Lohmann's own experiments on ATP, and Fiske and SubbaRow's, he got Lohmann to publish fast and steal a march over them, Fiske was sure.

Such 'accidents' are, of course, far from uncommon in the history of research. Fiske and SubbaRow's own interest in ATP sagged after the presentation and they went on to other fields.

But they had laid firm foundations for follow up work by others, that brought to light the full story of ATP, phosphocreatine and muscular contraction.

Here is the story and the implications, step by step.

Glycogen arrives in muscle. It is converted into lactic acid. Lactic acid is siphoned by blood to liver where it is re-synthesized into glycogen.

Three molecules of ATP are gained by the muscle in this whole cycle.

Glycogen breakdown is therefore the means of delivering food energy to the muscle in a ready-to-use form. But glycogen breakdown is slow to get started and only small quantities of ATP can be retained by the muscle.

Before fresh stocks of ATP arrive via glycolysis for renewed muscular activity, phosphocreatine serves as the reservoir of immediately available energy by re-synthesizing ATP as fast as the muscle uses up ATP's high energy component.

ATP has even entered medical practice. The Soviet Materia Medica advise *Acidum adenosintriphosphoricum* (ATP) in muscular dystrophy and atrophy, peripheral blood vessel spasms (intermittent limping, Raynaud's disease or paroxysmal spasm of the digital arteries and obliterating thromboangiitis), in chronic coronary insufficiency and dystrophy of heart muscles and for stimulating labour at childbirth.

The Trail Away From Harvard

Vilma Prochownick: A Jewish refugee from Hitler's Germany, she walked into SubbaRow's life one sunny morning like 'a breath of fresh air', cleared cobwebs in the lab and set his research mode while working for a couple of years as research assistant. Their dreams of scientific partnership evaporated when under the "magic mountain" spell of a hill-side TB sanatorium Vilma switched her passion from biochemistry to library science.
(From a 1934 passport, courtesy: V Proctor)

Harvard was the cradle of growth and flowering for him, without doubt. But he was outgrowing the cradle. Forces making him turn his back on his alma mater were gathering momentum in the years after phosphocreatine, marked by an equally intense involvement with finding a cure for pernicious anaemia.

This was believed akin to the killer disease which had struck his elder brother, the brother he was closest to.

Many factors contributed to his exit from Harvard. But they hinged round two of the *perennials in his life—financial low waters, and* the colour-cum-racial prejudice operating in the university.

The two factors were interlinked. Harvard, in the thirties and almost all through the forties, was simply not geared to the idea that brilliance was trans-racial and trans-national in its manifestation. Private and public stances on the issue contradicted each other with all the classic hypocrisy that surfaces when irrational fears deep in the psyche are stirred.

Privately, no faculty member or fellow

biochemist had two opinions about SubbaRow's brilliance. But private acknowledgement is one thing, and according public recognition to private knowledge quite another. For a decade after phosphocreatine and ATP, SubbaRow remained a Teaching Fellow. It was the lowest staff position and was usually reserved for graduate students. SubbaRow was a PhD degree holder from Harvard University!

Folin, Head of Biochemistry, did all he could, but was helpless against innate prejudices. In addition, the faculty wouldn't dream of entrusting student instruction to a coloured man, Teaching Fellow or not. Folin countered this by exempting SubbaRow from teaching assignments and keeping him as a full–time laboratory worker. He also raised his salary from 525 to 900 dollars a year.

SubbaRow was grateful to Folin. But his prospects remained far from bright at the time. A possible post as head of biochemistry in the Rockefeller-sponsored All-India Institute of Hygiene and Public Health in Calcutta had not materialised. His sole guarantee against unemployment and deportation was Folin. And Folin, as though punished by the gods themselves for his transgressions of the sacred boundaries of colour and race, died suddenly of a heart attack on October 25, 1934.

The event had far reaching implications for SubbaRow. A tussle over the successor to Folin broke out in the Faculty. Fiske was made acting head of the Department. Folin always put him in charge whenever he was away. Also, for some reason, he referred by name only to Fiske in the *Alumni Bulletin Review* of the joint research work of SubbaRow and Fiske.

Fiske's appointment, however, was not acceptable to the Faculty. Ever since the episodes that had robbed him and SubbaRow of full credits for phosphocreatine and ATP, Fiske had become moody and withdrawn. He was plagued, in addition, by a heart problem.

Laden with grievances as Fiske was, and given

HMS Biochemistry Dept, 1936: Albert Baird Hastings (1895-1987), new HOD, is at the centre in the front row. Although he had admiration for YSR as 'a most brilliant and dedicated biochemist', Hastings could not make up for all the past years of SubbaRow's stagnation in the Department. SubbaRow also did not quite fit into the profile of biochemistry envisaged for the Department by Hastings with his orientation to biochemical systems which contrasted with Folin's empirical biochemistry. Hastings could not, besides, give an Instructor who was not a member of the Faculty, facilities needed for the success of his research. (Photo Courtesy: I S Danielson)

Yellapragada Seshagiri in 1965, by when she had forgiven SubbaRow for not keeping his promise to return after three years at Harvard, realising her loss had been a gain to humankind. (Photo: S P K Gupta)

as he further was to dramatising the grievances rather than bearing them quietly, the Faculty felt he would be a difficult man to interact with. And as if bearing out these negative impressions, Fiske shut himself up in his room after taking charge, sending his greatly worried wife to SubbaRow for advice.

SubbaRow took up all the active work of the Department.

But a smear campaign against Fiske was started by the enemies that he had made by the dozen, thanks to his kinks. It began to be whispered around the Department that his contribution to research was overrated.

This was when SubbaRow acted in the impulsive way he could when higher principles were at stake. He wrote to the President of Harvard University, James B. Conant, on June 6, 1935, disclaiming all credit for the discovery of phosphocreatine and ATP. The operative part of his letter reads:

"My preliminary training was mainly in medicine and when I came under Professor Fiske in 1924, my knowledge of chemistry was very poor. As such I was merely an extra pair of hands for Professor Fiske and my contribution is mostly technical work. The brains behind the work, as well as the finer side of the technique, are entirely Professor Fiske's".

The fruits of paying heed to conscience and to the prompting of fair play were immediate.

Conant gave free rein to his likes and dislikes on faculty appointments.

The Medical School faculty had recently surrendered its rights of vote on appointments. Conant brought in as head of the Department an old friend of his, Professor A. Baird Hastings from the University of Chicago. Fiske was made a full professor. SubbaRow was left in the cold. Conant saw no reason to promote a man, who, on his own admission, was no more than an extra pair of hands for Fiske.

It was a cruel blow. SubbaRow had written the letter to clear the air for Fiske. He had written it with the confidence that his track record spoke for itself, was there for everybody to see and needed no trumpeting.

But it did.

The rules of the rat race apparently are the same everywhere, whatever the country or the times.

SubbaRow felt betrayed and let down.

It wasn't the best of times for him.

His association with Vilma Prochownick, the German expatriate who was his chemical analyst cum lab assistant cum lab caretaker, was drawing to a close. They had much in common. But they had deep and unbridgeable differences too that were bound to tell sooner or later. Vilma was just too European, setting store by the European values of uniformity, homogeneity and consistency in life. She couldn't understand how SubbaRow could

tolerate the maddeningly slow process of his self-devised technique of liver extraction from charcoal. Why couldn't he use vacuum pumps? Lack of funds was not a good enough reason for her. On the contrary, it should be cause to drive him to explore other avenues for getting the equipment. She, therefore, acting in typical no-nonsense European directness, spoke with Fiske and was told of the university financial crunch.

But the point is that this laissez-faire streak in SubbaRow, a biochemist of undoubted dynamism, was beyond her comprehension.

Other things baffled her too. His naive inability, for instance, to distinguish between the actor as a person and the character that he or she enacted. How good so and so was, in her role as a bad woman, Vilma would remark after they'd been to a play or a movie. What did she mean 'good', SubbaRow would object vehemently. How could a bad woman be good?

Again, SubbaRow fell into low spirits on being overlooked for promotion by Conant. Vilma happened to drop in at his lab. He would never get a faculty appointment in America on account of his race, he confided in her. Why, then, he wondered aloud, shouldn't he return to India where he could at least get the professorship that was his due?

It wasn't the money or the perks of professorship that was making him speak thus, Vilma could see. More than money it was recognition that he wanted, she saw too. And she saw, also, and commended, the sense of pride that operated below his selfless devotion to work.

But it still didn't fully square with the non-worldly aura that he had to him.

To a woman like Seshagiri these odd pieces in the jigsaw puzzle of his—or anyone's—character, would not have mattered, for she was culturally attuned to taking inconsistencies in stride. She wouldn't have given more than a passing thought to his equating the actor with the character that he or she portrayed. This is a typical trait of pre-modern mind sets that can be seen even to day.

Rama, Sita and Hanuman, enacted by human beings on TV or on the movie screen, are saluted with folded hands as though they are divinities taken avatar again in human form.

It was not that SubbaRow was pre-modern—it would be preposterous to say it. But vestiges of pre-modernism couldn't but tinge his cultural reflexes: internal evolutions are seldom total and seamless.

If he was a bit of a cultural curiosity to Vilma, she became totally incomprehensible to him in the way she reacted to the events that befell her. A pulmonary infection laid her low in 1936 just as the two of them were planning a joint career away from Harvard. She had to be confined to a sanatorium.

There, in the high altitudes of the sanatorium setting, the isolation and the mesmeric presence of the mountains, her perception on life underwent a sea change. She discovered English literature and the mystic vitalisations of living in the ambivalent zone formed by the interplay of the two realities of literature and life.

She wanted to give up science.

Was she mad? SubbaRow wrote to her in anger. He couldn't understand her sudden bent towards the abstractions of literature. Not that he didn't understand abstractions. But the abstractions of literature, especially fiction, foxed him, bamboozled him. Fictional characters, for him, never really came clear of their verbal acoustics in the way scientific principles did from their cauldrons of data: or in the way philosophical truths took form from the flux of life. Literature simply didn't move him enough. Nor could he understand her dogged insistence on being self-supporting. The war had broken out in Europe, and her parents could no longer support her. She wanted to do a course in library science to satisfy

her need for being among books. Unsuccessful in getting part time work for the money for the course, she borrowed it.

SubbaRow couldn't understand any of this. Why couldn't she throw in her lot with him completely, and come along with him as his assistant on a life time's mission of research?

They drifted apart, as they had to. Vilma married, and ten years later they did meet. She had mellowed. Perhaps she would have liked some kind of resumption. But SubbaRow couldn't make conciliatory gestures of that sort. When it came to close relationships he just wasn't flexible or imaginative enough.

In his dealings with Seshagiri, however, he showed a high degree of patience and an intuitive understanding of the psychology of a traditional marriage dutifully entered into and charged with overtones of the sacred. He felt responsible for her, compassionate even. But the divisive factors between them were just too strong to keep them united.

SubbaRow's restless and questing nature could not be contained by the domestic pleasures of life with in-laws and wife. His voyage to America was inevitable, foretold.

So was the tragedy of Seshagiri's life. Hers was the all too common story of a girl not given either the time or the chance to mature intellectually, emotionally or even physically, and yet enjoined upon by solemn vows to be accommodating to the man chosen for her. In the unformed, immature mind was thus implanted the ideology of destiny, wizening the girl. There's something schooled about Seshagiri waiting for SubbaRow's return. It is sad, even wrenching. But it is programmed, and therefore, not fully willed. It remains inarticulate.

The articulation came much later in 1941, in her 34th year. She'd had 17 years of waiting behind her, a period in which the voice of personal perception and individual will had been quietly forming beneath the formal and externalised grief. This embryo voice broke out in the open when SubbaRow sent her 2500 dollars along with 6500 dollars to her father in repayment of the loans he had taken from him for his fare to America and stay and expenses there in his first struggling years. His cash reserves were up in the post-Harvard period that he had entered at last. Why is he sending me money, Seshagiri wondered; aloud, gaunt with the years of the ascetic living laid down for women in her circumstances.

'What I want is him', she thought next, as she told SubbaRow's biographer S P K Gupta. This wish was not ever to be gratified, she saw with a dry-eyed, newborn clarity of vision. But the money proxied for him. She related to it as to his live presence with the vicariousness that only a woman of her cultural background could muster. One cannot imagine Vilma doing this. From this union of memory, recall and acceptance of her lot and her circumstances, new ways of relating to the reality around her suggested themselves to her. The money that finally came to her after SubbaRow died intestate in 1948 was a tidy fortune — 15,000 dollars. She spent it all on the education of her many nieces and nephews. She felt fulfilled. And she could look at SubbaRow's work with the detachment she could not earlier on. She put it in a characteristic mix of fatalism and the calmness of sublimation: 'It is my misfortune that he never came back. But our marriage served to fulfil the mission of his life,'

The marriage lives in those words. It is a form of life that only she could give. She culled it from the alloy of the never-had-been and the living reality of a present resulting from the never-had-been. An alloy that only she could forge. It was *her* triumph. SubbaRow's was the negative though necessary contribution of sustained absence.

SubbaRow's marriage with Seshagiri, to sum up, was one more of the many failures and setbacks in personal relationships as well as professional prospects that he was beset with at this time.

The Road Uphill

Milton Elkin, Professor of Radiology, Albert Einstein College of Medicine: As an undergraduate with biochemistry as his elective, Milton first synthesised nicotinic acid analogues for SubbaRow who helped him gain entry into the Medical School, where a student fellowship helped him to work again for SubbaRow in the summer of 1939. Having done the library research, he was cited along with HOD Hastings as co-author of SubbaRow's review paper in a German journal on the search for the anti-pernicious anaemia factor in liver. SubbaRow was troubled when only his own name appeared as author of its summary in Bangalore's *Current Science* and wrote an apology to Elkin who had by then joined USAF, declining SubbaRow's offer of a war-related job in Lederle Laboratories that would have granted him exemption from the draft.
(Photo: S P K Gupta)

The handicaps under which SubbaRow was functioning began to come into sharp and telling focus now. He had no facilities for testing the liver fractions he got from his labours in the laboratory. For testing he was dependent on collaborators who were diligent but, with different aims, followed methods they thought best. SubbaRow had little control over them, for they were not graduate students under his direct supervision but medical students doing part time in his laboratory to see them through their courses. Not only this: he was dependent on facilities in Pearl River for any large-scale isolation work he had to do. And for chemical analysis he had to turn to a commercial laboratory way out in Arlington, Virginia.

Despite these handicaps there was no slackening of ardour on his part to follow up promising new vitamins that surfaced in the course of his mission of charting liver for the clue to pernicious anaemia.

The anti-pellagra vitamin was one of these promising trails. Some of the fractions were beneficial to both pernicious anaemia and pellagra patients.

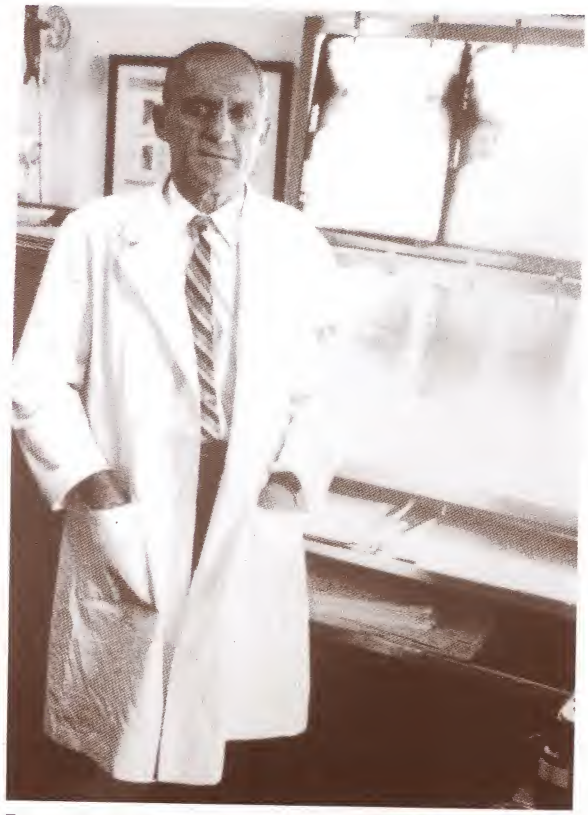
Joseph C. Aub, of the Harvard Medial faculty, regretted that SubbaRow suffered socially and academically as Harvard at that time was isolationist, did not encourage non-Americans getting a good position in the faculty. (Photo: S P K Gupta)

There were snags, though. For one, where were the pellagra patients to come from? Pellagra was no widespread malaise in the prosperous New England region from where SubbaRow operated. Fortunately it was demonstrated by the US Public Health Services that the nutritional deficiency for both black tongue and pellagra was the same. This meant that promising pellagra fractions could be first tested in dogs afflicted with black tongue. But it was far from smooth sailing yet. He needed dogs in scores for tests. Boston veterinarians helped out. From this collaboration resulted a yellow crystalline material that seemed to augur well for black tongue afflicted dogs.

But Fraction C, as this material was called, had to be supplemented by an unidentified peptide for full cure. Some forty dogs afflicted with black tongue were tested. But nothing conclusive came from the tests. And after this, further tests didn't seem possible because the Boston veterinarians couldn't keep up with the task of inducing black tongue in dogs for SubbaRow's experiments.

SubbaRow had to seek help from veterinarians in other quarters. South Carolina was one such place he repaired to. Tests conducted in Hartsville by a Dr Lawhon indicated that not Fraction C but the waste material from the manufacture of liver extracts for pernicious anaemia was where the curative factor for black tongue lay. But again, nothing conclusive came from the tests.

The momentum did continue for some time, though. For the reports of the southern universities caught the interest of Tom Spies, the physician in charge of alcoholics in Lakeside Hospital, Western Reserve University, Cleveland. The alcoholics were often pellagra-afflicted too, with a high mortality rate. Collaboration now began between SubbaRow and Tom Spies. Spies found that Fraction C given along with the main liver extract led to impressive cures for pellagra patients. This was cheering. But differences soon developed between the two men. SubbaRow



Edward Meilman, Chief of Medicine, Long Island Jewish Hospital: A medical student who had several research assignments in SubbaRow's HMS lab, he regarded SubbaRow 'the greatest intellect to whom I have been exposed in my entire life'.
(Photo: S P K Gupta)

wanted a definite feedback about the compound that Spies found 'potent'. Also, he feared a mix up because Spies was testing other materials too that he was getting from diverse sources. SubbaRow got no satisfactory answer to any of his doubts or queries. Spies virtually told him to mind his own business. The patients were his, he said, even if the material was SubbaRow's.

SubbaRow now turned to North Carolina, to the coordinated pellagra project at Duke University, Durham, being financed by the Rockefeller Foundation. Two teams were at work on the project headed respectively by Dr David T. Smith and Dr W. J. Dann. The teams were supposed to work jointly. But in actual practice they worked independently. Neither group informed SubbaRow of this. The data he got from them was confusing. Was only one nutritional factor needed for the cure of black tongue and pellagra, or more than one?

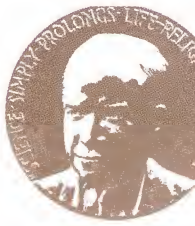
William Berenberg worked in SubbaRow's lab while a Harvard undergraduate and was helped by him to enrol in Medical School. He teased SubbaRow on leaving for Lederle: "Finally you have seen the light ... May be you have your own catalogue now and will be able to get some of those things in life." He got the reaction: "This is an opportunity to be creative in a laboratory. Not so much a question of personal finances. It is a chance to work without being concerned about budgets for work." (Photo: S P K Gupta)

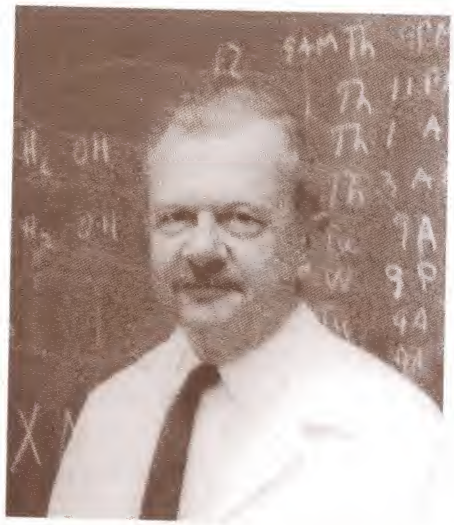
SubbaRow, nonetheless, went ahead with his fractionation work and came up in 1936-37 with nicotinic acid. It was *the* cure for black tongue and pellagra. But the tests that were made to confirm it turned out into a series of goof ups that robbed SubbaRow of the laurels he deserved. Dann tested nicotinic acid and two other nucleic acids SubbaRow isolated from liver. He reported negative results.

Dann's faux pas lay in not testing nicotinic acid against black tongue after it failed against chick pellagra and rat pellagra. He was influenced in this decision by the conclusion of a team of nutritionists under Conrad A. Elvehjem of Wisconsin that black tongue and chick pellagra had the same preventive factor. This was against Dann's own observation earlier that these ailments were distinct from each other. But he allowed himself to be influenced by Elvehjem. Elvehjem himself did a volte-face on the black tongue-chick pellagra identity. This happened from the very tests he undertook to rule out once and for all that nicotinic acid was effective in black tongue. He tested it on his own litter of dogs. And the tests were positive!

Hurriedly Elvehjem announced it in the September 1937 issue of the *Journal of American Chemical Society*. SubbaRow, the original discoverer of the vitamin properties of nicotinic acid, was nowhere in the picture in this formal announcement. And Elvehjem had conducted his tests after a discussion with SubbaRow!

SubbaRow was stoical. More tests were carried out on black tongue dogs by Dann, Mrs Susan Smith, the nutritionist in one of the two teams at Duke University, and doctors at the Indianapolis City Hospital, and Tom Spies, the





A M Brues, Director of Biological and Medical Research at Argonne National Laboratories, secured from SubbaRow, while they were at Harvard, amino-ethanol, a growth retarding fraction from liver for testing in tissue cultures. He found SubbaRow had in his small lab many reactions going simultaneously —boiling, distilling or being centrifuged. Like a chessmaster playing simultaneously with several players, SubbaRow went around attending one after another to each reaction even as he kept up discussion with visiting research collaborators. (Photo: S P K Gupta)

very Spies who once had told off SubbaRow when he queried him about his methods of testing. All these tests now proved positive. There was no doubt about it. Nicotinic acid was the cure for black tongue and pellagra!

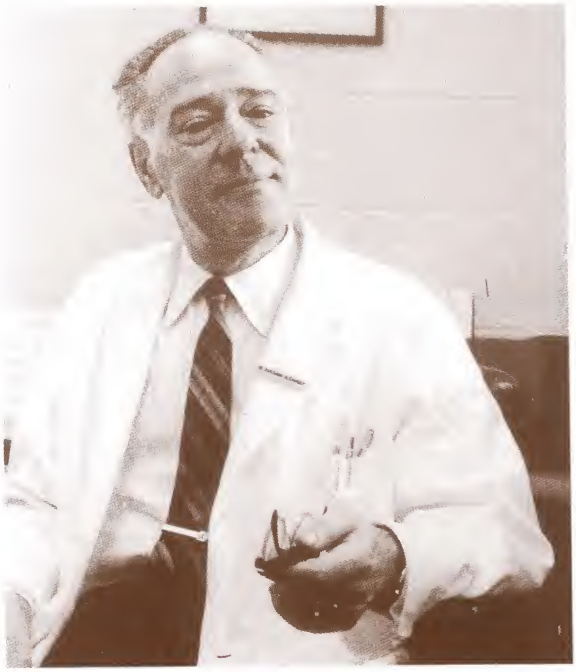
Within a year -- in June 1938 -- SubbaRow suffered a second time from the absence of testing facilities of his own. The genesis of the trouble, this time, lay in the fact that nicotinic acid, unlike whole liver, was not proving effective in the treatment of relapses of black tongue occurring after a second attack was cured. This was the finding of clinician David Smith in one of the two groups working on anti-pellagra at Durham, Duke University. This led Dann, the leader of the second group, to wonder if liver couldn't yield a vitamin still better than nicotinic acid for curing black tongue and pellagra.

SubbaRow, accordingly, sent to Dann through Clark of Lederle a supply of beta-aminopyridine. Dann sent back highly favourable reports after testing it on black tongue dogs. SubbaRow and Dann, thereupon, published a report in the *Journal of American Chemical Society*.

But the preparation proved ineffective in pellagra patients. Also, subsequent tests on black tongue dogs by SubbaRow, Dann and Elvehjem yielded negative results. Beta-aminopyridine was simply unable to repeat the cures Dann had observed in his initial tests. There was no explanation for this. A retraction had to be published. SubbaRow and Dann, thereupon, published one in the *Journal of American Chemical Society*: "It is clear that our earlier conclusion is incorrect and beta-aminopyridine is not a black tongue preventive factor".

SubbaRow's fortunes were at low ebb in every way in this period just before his departure for Lederle. His staunch friend and clinical collaborator, Jacobson, tried to pull strings in favour of Suby by informing the President of Harvard University, James B. Conant, of forces at work that could make SubbaRow leave Harvard

Max & Betty Tishler: Max and Sub were kindred souls. The marriage of the Tishlers was saved by Sub's counselling. Their son, Peter, became a physician as predicted by SubbaRow at his birth.
(Photo: S P K Gupta)



Benjamin Alexander, who rose high as internist at Boston's Beth Israel Hospital, considered SubbaRow a veritable scientist-genius, a *guru,* whose picture at Stockholm's Karolinska Institutet indicated his having been considered for a Nobel which, he is sure, would have been given to him if only he had lived longer. (Photo: S P K Gupta)

for what would be considered greener pastures. He had offers from Columbia University and Albany Medical College, Jacobson said to Conant. He added that SubbaRow was not really inclined to take one of the posts unless he was driven to it. Wasn't it Harvard University's duty to retain a biochemist of SubbaRow's stature and renown at all costs? Should the forces that could drive him to leave be allowed to prevail?

Conant did rise to the occasion. He promoted SubbaRow to the post of Instructor from Teaching Fellow, and raised his salary to 2400 dollars. More he could not do without trespassing into the domain of the head of the biochemistry department, A. Baird Hastings. And Hastings's orientation to biochemistry was different conceptually from that of Folin whom he had succeeded, and under whom SubbaRow had trained. Not that Hastings was not sympathetic to SubbaRow. But as Instructor, SubbaRow was not a member of the Faculty, and Hastings therefore could not give him the facilities he needed for his research. He did bend rules to the extent of asking SubbaRow to take classes of medical students, thereby making a dent in the age-old prejudice against entrusting coloureds with teaching responsibilities that held sway in Harvard.

But SubbaRow's accent was incomprehensible to the students. They said his English sounded like an Indian language.

A deeper reason for his lacklustre performance as teacher lay in the long, cloistered years he had spent in his lab, where he did teach students, but naturally not as a classroom exercise. Harvard had to make up for a lot of neglect it had heaped on this brilliant, non-white biochemist in its midst. It simply wasn't mentally equipped to do this restoration job in the grass roots way it had to be done. It couldn't give him the professorship he deserved in every way, couldn't give him the facilities he needed for his researches. Half-way measures were all it could or would make.

Harvard University's inaction, whether from conscious or unconscious reasons, strengthened the case for SubbaRow's exit.

However, for a man who had dismissed home and family life as effete interferences in his pursuit of non-family, non-domestic, cerebro-spiritual interests, SubbaRow was unbelievably, touchingly, concerned about his co-workers' family lives. With all of them he was on easy, visiting terms. By virtue of temperament, as well as the detachment that his cultural otherness gave him, he was a guru figure to his colleagues. He could advise them on family problems, channelise their professional talents, generally straighten out things for them. When Max Tishler, chemist, had his first child, SubbaRow was at the hospital, extending the moral support that the young couple needed. Almost all his colleagues were Jewish. With the

Jews, SubbaRow struck easy rapport. They had little colour prejudice. They were poor, like him. The involvement of the members of the group with one another rose solely from the impersonal yet binding power of their professional commonness.

It was a happy group life that SubbaRow had, by and large. It bred its own solidarity and a desire for corporate self-perpetuation. SubbaRow wanted the whole group to go with him when he left Harvard for Lederle. He wanted the good work and the companionship to continue. A few did go with him. Those who didn't then, did, later. Many collaborated with him from the institutions where they found places. And all, without fail, acknowledged his charisma.

But charisma can be harmful. It can inhibit growth in others. Benjamin Alexander was one of those who resisted it, and breathed a sigh of relief when SubbaRow left: "It left me as a young scientist to swim alone. Otherwise I would always have swum on his back". But Alexander too worked for Suby after he left Harvard.

Nonetheless, this happy group life didn't encompass all of SubbaRow. It couldn't. As the only wife-less and family-less member of the group he had spells of solitude to fill up as best as he could. These spells brought into focus his underlying state of isolation and not belonging. For all his friendly, visiting relationships with his colleagues he couldn't really be in the picture when they were acquitting themselves as husbands and fathers. Lunch hours, for instance, were often family gatherings, and they would drive off home. SubbaRow would wend his way to the store room to eat his sandwich lunch with Mr Martin the storekeeper, packing cases strewn all around. He didn't have the rank to join the faculty members for lunch. He was just the coloured immigrant in these hours.

That harsh reality was never too far from his immediate consciousness. As a coloured immigrant he had to have his work permit renewed at regular intervals. He lived in dread of being picked up and deported for committing some minor infringement of the law. And one night it nearly happened. A woman had been molested in the area where he lived. The police took one look at him and decided he was the malefactor, and put him behind bars. He was released in the morning. But it seemed like the end of the world for him.

Underpaid, under-recognised but touchingly cheerful with colleagues of limited means so much like himself, SubbaRow was ripe despite himself for the overtures from Lederle.

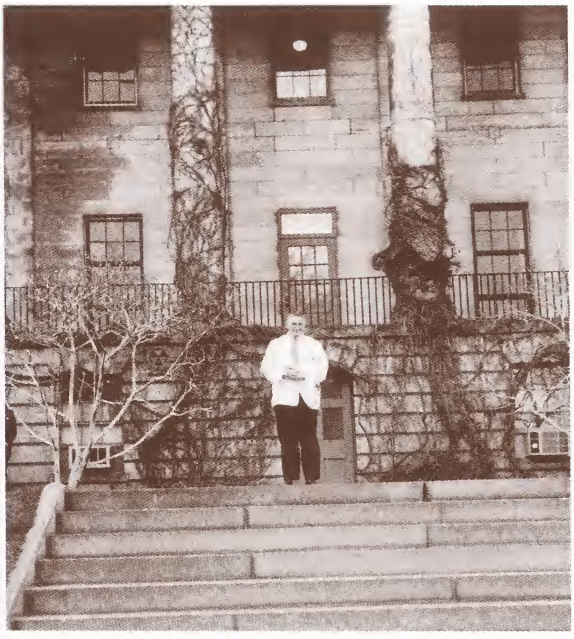
Coming To Grips With Anaemia

William P. Murphy, Boston Physician, won a 1934 Nobel with George Minot and G Whipple for whole liver therapy of pernicious anaemia. He clinically tested SubbaRow's injectable liver extract, the standard and still the best treatment for pernicious anaemia although Vitamin B_{12} is now the preferred treatment. (Photo: S P K Gupta)

In the 1930s, as we saw, just a few months after his formal presentation of ATP at the 13th International Physiological Congress, SubbaRow was up to his ears in trouble with problems on both the family and professional fronts. Seshagiri's people had intensified their efforts to get him back home. And SubbaRow, as usual, was unable to balance the demands of wife and work. He did make efforts though.

He'd got his Ph.D. from Harvard in February 1930. On the strength of it, and on the advice of colleagues, he entered the race for the biochemistry chair in the All India Institute of Hygiene and Public Health, proposed to be set up in Calcutta by the Rockefeller Foundation. He had little chance of getting it because the British were not keen on having Indians at top posts, scientific or whatever. An offer did come from Dr William S. Carter, the Rockefeller Foundation coordinator for the Calcutta Project. But SubbaRow wanted an assurance of complete freedom of research from the director-designate of the Institute, Lt Col Alexander D. Stewart.

Stewart did not reply to SubbaRow's letter. Any guarantee of any kind to a prospective



Bernard Jacobson (1965) before MassGeneral Hospital's Malinckdrodt Ward-IV where he conducted clinical trials of SubbaRow's anaemia potions from liver extracts. (Photo: S P K Gupta)

employee, however deserving, did not square with his rigid cast of mind, correct to a fault.

SubbaRow wasn't really keen on the job. It was just something he'd allowed himself to be talked into. Harvard, his alma mater all said and done, left him alone to pursue his research even if it was without any extra remuneration apart from the measly salary he got from his teaching assistantship. But he could honestly tell Seshagiri and her people that he would return home if he got the Calcutta job. He thus bought time and respite from their pressures even though he did not for a moment deny the legitimacy of the pressures.

But he was not keen on the job, most of all, because he was on the verge of a breakthrough in isolating from liver the vitamin that cures pernicious anaemia.

This disease was then believed to be akin to tropical sprue, the killer disease which had carried away his eldest brother, and afflicted all his brothers and himself.

As early as September 1927, SubbaRow had met a kindred soul, Gordon A. Alles, engaged like him in liver fractionation work. Working with Dr Edwin J. Cohn, the authority on protein chemistry, Alles used the method of heat coagulation to remove protein from liver whereas SubbaRow used trichloroacetic acid. The difference kindled mutual curiosity and interest. Alles's immediate task was to provide more palatable liver material for the pernicious anaemia patients under the care of two Boston physicians, Minot and Murphy, who had turned to Cohn for the job. They had found that broiled liver did wonders for the patients. But broiled liver was foul to look at, in addition to being foul to the taste, and the patients, already suffering from lack of appetite, resisted the stuff. Also, the necessary dosage of one hundred grams was too much to take in. Alles and his team reduced the dosage by removing all inert material from liver. They were presently engaged in isolating the pure, clinically active substance.

SubbaRow was, of course, highly motivated to work on the isolation of APAF (anti pernicious anaemia factor). For he wanted to avenge the death of his brother. But he could not tresspass into research area already staked out by the Cohn-Alles group in the same university. It was professionally unethical. Bernard Maxwell Jacobson, his research partner, suggested using animals for tests. Since the Cohn team was using humans for tests, there would be no competition between the two groups, he said. They -- Cohn and Alles -- could use in humans the liver fractions which gave positive results in the animal tests.

Fiske, SubbaRow's senior, was not happy with this solution to the ethical problem. But he was willing to go along as long as SubbaRow researched on APAF as an independent project of his own. That meant, of course, that the funds, time and facilities were only such as could be spared from the official research on phosphorus compounds.

Mallinckrodt – Ward IV: Commemorated in an eponymous book, it was here that Jacobson effected his first cures of pernicious anaemia with the injectable liver extracts that SubbaRow cooked up in his lab. (Photo: S P K Gupta)

It had to be work on a shoe-string budget, in other words.

Both SubbaRow and Jacobson now plunged into liver fractionation work with frenzy. They raided the butcher shops of Boston to stock up on liver -- to the glee of the butchers who were only too happy to unload their otherwise unsalable stocks at the special price they were being paid.

Back in the lab they set to work cooking, boiling and messing around with the liver, coming up with potions of various stinks and colours. They fed these potions to guinea pigs, took out blood samples, counted the red corpuscles, all in meticulous fashion.

A break in this rhythm of work occurred when Jacobson had to leave on assignments connected with his medical career. Earlier, in 1928, Alles had left Harvard for doing work on insulin in California. Two years later, in 1930, Cohn himself left the field for doing work in amino acids and peptides.

With the departure of the two fellow chemists who were making his own efforts in APAF ethically questionable, the field was now clear for SubbaRow to go full tilt.

But Jacobson's departure and the constraints of time and money already there did not contribute to much progress.

In the autumn of 1930, however, a replacement for Jacobson came: Gared Y. Garber, a second year medical student. Together, they made a very crude form of high potency liver extract. Now it was a question of testing this extract and further refining it. Happily for SubbaRow, Jacobson came back from his assignments in Europe, to work as a full-time clinical collaborator.

The crude liver extract was very effective in guinea pigs. Through successive tests they devised a standard minimum of liver material, the Guinea Pig Unit, which by a single injection raised the red blood corpuscle level in a guinea pig weighing

joint paper on Fraction I, which was the most potent anti pernicious anaemia factor todate, in the *Journal of American Chemical Society*.

Further processes of concentration and reduction of dosage, nonetheless, went on apace. A few months earlier, Jacobson had found that a combination of three liver fractions was highly beneficial to pernicious anaemia patients. Only 12 to 15 mgs of the solid substance was required per injection as against the 180 mgs of earlier preparations. One c.c. water solution of the combined fractions was as effective as 100 grams of the liver treatment prescribed early in 1926 by Minot and Murphy.

. A little later, in June, Lederle Laboratories, the pharmaceutical company, marketed 'Lederle 1 C.C Liver Extract' for pernicious anaemia, and 'Lederle Hepatic Extract' for black tongue in dogs.

The drug was the outcome of strong connections that were developing between Dr Guy W. Clark of Lederle Laboratories and SubbaRow, as if presaging the day when he would finally leave the sedate, academic environs of university and hospital for the competitive, quicker air of the pharmaceutical concern.

Clark had initially sought technical advice from SubbaRow in return for a steady supply of crude liver extracts. A high watermark in this friendly barter system was reached when Clark made available to SubbaRow the vacuum pumps he badly needed for his work of extracting liver substance from the charcoal, that he added to the solution for clinical purposes only to find that it soaked up the liver.

Fiske also played a part in this event. Clark had gone to see Fiske about a liver preparation Lederle was marketing that had developed chemical problems. In the course of their discussion a reference to SubbaRow came up. Fiske was as yet affable and not the cantankerous person he turned into later. 'Do something for him,' he stormed at Clark. Here was this brilliant biochemist from India, spending hours cooking 30 to 40 pounds of liver every day on primitive equipment, thanks to the financial crunch in which Harvard University permanently laboured. Why didn't Clark do something for this brilliant, resourceless scientist? What was he doing with all the fancy equipment he had at his disposal in Lederle? Send Sub the vacuum pumps he needed for his distillation work, Fiske harangued Clark.

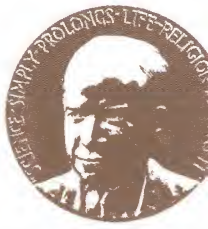
The pumps arrived soon after.

Further concentration of Fraction I was impeded by speculation about the enhanced curative effect of the main active liver fraction, Fraction I, or the primary factor as it was called, to which certain other substances, that had come to be known as the *accessory* factors, were added. Jacobson in his clinical trials had isolated some of these latter which seemed to supplement the action of the primary factor in pernicious anaemia therapy. SubbaRow summed up these possibilities in a 'Multiple Factor Hypothesis'. Whether, and to what extent, the accessory factors affected the curative strength of the primary factor was to remain an unresolved question for the next eight years.

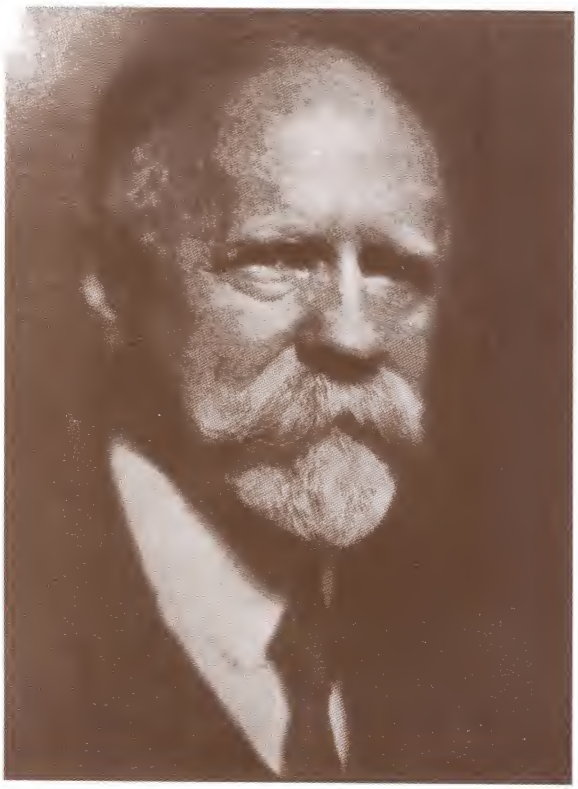
The problem, basically, was inadequate data. Doctors did not know at that time — the early 40s — that APAF was present in liver in micrograms, not milligrams. Fraction I had cut the liver dosage by one to one hundred thousand. Less than one milligram of it was as effective as the one hundred grams of raw liver originally prescribed by Minot and Murphy. But a milligram has more than a thousand micrograms and micro techniques were just not there to measure out micro measures.

SubbaRow, Jacobson and the rival biochemists of other schools in Zurich, Oslo and New York engaged in APAF work sparred with each other. And they published their views in careful, balanced and inconclusive terms in the scientific journals of the day or at medical conventions.


SCIENCE · SIMPLY · PROLONGS · LIFE · RELIGION · DEEPENS · IT
YELLAPRAGADA SUBBAROW
1896-1948
SCIENTIST · TEACHER
PHILOSOPHER
HUMANITARIAN
DIRECTOR OF RESEARCH
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY



Good Bye At Last



William Brown Bell, President of American Cyanamid. With the starry-eyed research promoter laying his odds on him, SubbaRow could make Lederle a pharmaceutical leader.
(Photo: Lederle; courtesy: Sisir Mitra)

When William Bell, head of American Cyanamid, asked SubbaRow to join Lederle Laboratories, which his corporation owned, he was offering him 15,000 dollars a year. It was a colossal amount for SubbaRow, a steep rise from the 2700 dollars a year he was getting at Harvard. But this kind of crass arithmetic was not, could not ever be, the deciding factor for him. He wanted a new research building for his work at Lederle more than a high salary, he told Bell. He said he was prepared to come for half that salary if a lab was guaranteed.

Bell agreed to this condition, though it could not ever be said of him that he was stingy and was trying to get a top scientist cheap. SubbaRow, on his part, tenuously and belatedly woke to everyday wisdom after volunteering a cut in salary. When Hastings, his departmental boss, asked him, 'Sub, how much is your salary going to be?' he was sheepish, evasive.

Salary wasn't discussed, he said.

The fact, of course, was that money hardly ever figured in his calculations as a means of personal indulgence, of the 'good life'. He needed money and in unlimited, unquestioned amounts,

SubbaRow, the MD to the PhDs and the PhD to the MDs. (Photo: Lederle)

for work purposes. And for procuring this kind of money he had Wilbur Malcolm, administrative head of Lederle, as his trusted champion.

With Bell, he had different problems to settle, more intrusive than money. Bell had an adolescent and starry-eyed infatuation with science. It made him an inveterate memo scribbler. Ideas of cure and rejuvenation from whatever source – press, hearsay or direct observation– flooded his brain like storm waters. And he would send off deluges of notes to SubbaRow.

He did give these notes a touch of the burlesque, though.

"Would my entries in a horse-show look better if given Lederle Vi Delta or Vitamin B Complex for a month or two beforehand? Do cows give more and richer milk, do hens lay bigger and better eggs when assisted by Lederle products? I suspect that the answers to these questions are not yet known but I recommend that we experiment.'

Most times SubbaRow simply scribbled on the notes, 'No reply necessary', even though the notes with the bantering tone would be kept up. But Bell was, all said and done, the Chief, the big boss, and even his banter could not be dismissed off hand: not even if he himself said, as he did: "If I occasionally threaten the freedom of scientific thought by suggesting a bright idea for a research project, it is promptly but tactfully treated with the contempt it deserves. However I refuse to believe that these suggestions do much harm."

Wasn't there the faintest but unmistakable tone of seriousness in the last sentence? SubbaRow was extra sharp of hearing in those beginning months in his new work place!

Bell's teasers led to real irritants when others in the company hierarchy tried to imitate him by coming up with their own bright ideas. Somebody came up to him with the idea that the company enter the field of baby foods, digested cow's milk and injectable foods. SubbaRow tartly referred him to a Director, R.C. Gaugler, 'whose capacity for accumulation of data seems to be unlimited'.

All these irritants and pinpricks of course got absorbed, finally, in the even tides of routine. But not without an initial, uncomfortable period of coping. The fact, basically, was that the company simply could not afford to lose SubbaRow. It was a difficult transition period through which Lederle was passing. For the very industry of pharmaceuticals was in the throes of absorbing the tremendous discoveries being made in nutrition and antibiotics. Lederle could not survive, or weather these unfolding, still uncertain times, without a firm footing in turnover, coupled with a clear forward vision. Both Bell and Malcolm knew that such superlative guidance could not be provided by anyone except SubbaRow.

They cherished and valued him. Bell's innate humanism woke in the pathos surrounding this young associate director of research, uprooted from country and kinsmen, who had pledged his loyalty and commitment to the fortunes of his employer's company. Fond feelings rose in the wake of the pathos. The urge seized Bell to dispel the film of solitude that stayed round SubbaRow. He showered him with company and warmth and

Dr Wilbur Malcolm, Director of Lederle Laboratories: He fought with the vice-presidents and got the money SubbaRow wanted for his research, and was vindicated by the products SubbaRow brought out. The two made a great team.
(Photo: Lederle; courtesy: Sisir Mitra)

care. He raised his salary to the original figure of 15,000 dollars he had proposed. He strained to make up for the recluse's life he had been consigned to in Harvard.

SubbaRow could not respond to these gestures with the spontaneity Bell would have liked, and perhaps expected. Never socially spontaneous at the best of times, his reclusive tendencies had come to the fore once again in these early years at Lederle.

But Bell's goodwill gave him the level field he needed for carrying out his research programme.

A path-breaking eight year period lay ahead of him, in these last eight years of his life.

The Cheerful Recluse

Anne Schivek-Mowat, the lab assistant in Boston, who followed SubbaRow to Pearl River as junior biochemist, discovered biotin in fumaric acid fermentation broths. Illness ended her promising scientific career. (Photo: S P K Gupta)

SubbaRow's loner ways increased in his new surroundings. On the work front he was totally giving. He gave not only in terms of hours of work, but in the more binding and ennobling terms of fostering selfless attitudes to work among his team. His definition of selflessness was extreme, not one capable of winning unopposed acceptance. It was denunciatory of marriage, family, and all the emotional commitments that a man enters into, driven by urges all too human. These commitments were sapping, he said. They were a waste of precious time. They were not worthy of a man. These were some of the things he had to say about them.

Nonetheless, he did concede the rights of wife and family to a slice of the man's precious time. When a team member, Jim Boothe, got married he at first flatly refused to give him leave for a honeymoon. But later, on second thoughts, he relented. He gave him a week! Between family and work he never did manage to build bridges, neither in his own life, nor perceive it in the lives of others through empathy. But he was forever conscious of the turbulent extra dimension that his

team-mates had to their lives, and which stole their loyalties from work. He couldn't ignore this turbulence, couldn't really deny the sustaining and therapeutic powers it had for its incumbents.

He therefore turned propitiatory of it, kept it mollified, and thereby confined it to the background — the spaces where he felt it belonged. His method was to overpay his staff — not too much but enough to surprise the wives, and deprive them of grounds for bickering. And secondly, he encouraged outings and picnics and family parties in which work took a back seat. He himself never joined these parties. His sense of responsibility for, and involvement with, his staff didn't extend to participation in their off-duty revelries.

The intense and vigilant sense of responsibility he had for his staff often found expression in extra-sharp retorts. When his men were making the special intermediate compound needed for synthesising Teropterin, for instance, he was always at the door, watching them at work. What was the idea, one of the men burst out in exasperation. 'I am watching the blood vessels of your eyes,' SubbaRow replied. If they inhaled too much of the hydrozoic acid that was liberated by the hydrazine hydrate used by the men for the intermediate, it practically spelt the end. The reaction started with irritation of the eyes and the mucous membrane. Then it led to kidney and spleen injury, ending in convulsions and death. If too much of the highly poisonous gas had been inhaled, he said, he could 'tell by the size of the blood vessels in your eyes, and I would throw you out'.

But even without participation he was a man who couldn't be kept out of the mind long. His personality had a natural dominance. His ideas, views, perceptions and perspectives — his whole intellectual-spiritual make-up and the composition

SubbaRow in the backyard of the apartment house with Danielson, another admirer cum devotee from Boston, and his kids Kenneth and Robert. (Photo courtesy: I S Danielson)

of his sub-conscious, in short, were so different that they occupied the thoughts of all those who came into contact with him, all those with whom he interacted, so that he was the topic of conversation of the revellers.

He had a hold over the minds of his boys; there was no doubt of it. It gave him a certain freedom of action. He could give full expression to his natural dislike of hierarchies of any kind — educational or social. He didn't think a PhD was any hard and fast sign of superior intellectual endowment. He fixed salaries for his men depending more on their innate and latent capacities than on their paper qualifications. PhDs and non-PhDs thus often got equal pay much to the heartburn of the PhD's. His recruitment policy was also off beat and flouting of established practices. He could link recruitment to potential. George Krupka, for instance, came in as a graduate in mathematics, fascinated by SubbaRow's lab, chucking up his job in his uncle's construction company. He could get in only as a janitor. But SubbaRow didn't forget that he was a graduate. He personally trained him in isolation techniques, and saw his protégé grow into one of Lederle's leading fermentation chemists.

His belief in hard work was different from the American belief in it. The latter's was a little too success-oriented, a little too exchange-based, for his taste. Hard work was for him a tool to dispel the dark areas in man's knowledge of the universe, of the awesome and stupendous spread of the objective reality around, of which he was but a part. It was a life-long quest into the terrain of the unknown.

This assumption of prior smallness went against the grain of American-Western thinking that was pyramidal in concept, and set man at the apex of the pyramid. It spelt a basic difference in the approach to science. It threatened to lead to serious impasses in the Research Committee of Lederle, of which SubbaRow was only one of the members, in the beginning. Formally, though research and administration were both under his control.

His chief trouble-maker was Austin Joyner, who held in esteem everything that SubbaRow did not. Degree and rank mattered to Joyner. The MD was a natural superior to a Ph.D., he held. It was intolerable to him that SubbaRow, a mere Ph. D in chemistry, should be directing research. It came down to the personal level soon enough, as it had to. Why was the budget for SubbaRow's department growing, he asked.

Things took a turn for the worse in the spring of 1942, when SubbaRow brought over his old friend in Harvard, Leo Rane the bacteriologist. Joyner saw it would strengthen SubbaRow's bacteriology group as against his own. And SubbaRow would depend less on him, Joyner, for clinical investigations, as Rane had connections with hospitals and medical colleges. Joyner decided to quit and join the Army Medical Corps. And he taunted SubbaRow for not doing so himself. He was untrue to the country where he had come to live, he said. He wasn't man enough to die for it, could only live off it. He was a traitor, exactly like his compatriot Gandhi, who fought the British for his and his country's right to abstain from the war effort.

He left. His department came under SubbaRow. And, in October 1942, he was made Director of Research.

He could now plan and execute his research projects in ways he thought best, without having to explain his concepts of science or his approaches in inter-personal management to vainglorious challengers.

But it was still not smooth sailing automatically. A major confrontation was on the cards with Thomas Hughes Jukes, a specialist in animal husbandry, who fought for his proteges in SubbaRow's department with politically motivated vehemence. In the second place, new

recruitments to his team went on, in pace with changing research objectives. A problem of integrating the new members with the old seemed endemic. The new ones tended to monopolise his attention, understandably enough. And, understandably enough too, the older ones resented this shift. They sulked, silently rebelled against his assumptions and ideals. They wouldn't work longer hours, wouldn't burn the midnight oil easily any more. They weren't impressed by his argument that as those exempted from military duty they had a moral obligation to put in as much sweat and toil in their work as the soldiers at the front.

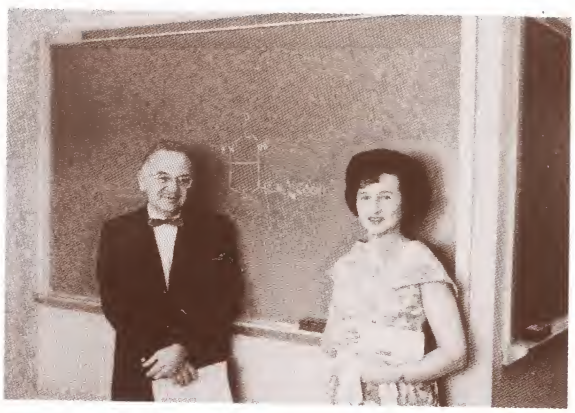
Added to this was the fact that salaries in the lab were just about the minimum that industrial workers got. Exoduses and exits to rival laboratories like Merck, which paid much more, became common.

But SubbaRow didn't change his style of functioning. With his clever and insightful mix of individualism and group spirit, he kept his team at a creative high most of the time, despite the disgruntled elements and their cribbing.

All his path breaking achievements in Lederle Laboratories came from this medley cum compact assemblage he built and sustained by the sheer strength of his personality.

Thomas Jukes, who came as Associate Director and was made 'nutrition consultant' when he introduced politics into the healthy scientific rivalry in SubbaRow's research team. (From a Lederle Laboratory notebook)

Learning The Ropes About Patents



B R Baker, who synthesised biotin (formula on blackboard), with Mrs Baker. (Photo: S P K Gupta)

SubbaRow came to Lederle in May 1940. From then till the end of 1943 his energies were spent in the lesser task of synthesising vitamins already discovered by others. These processes were to be presented to Lederle as exclusively theirs, with full rights of patent. He was promoting Lederle's interests, Lederle's image and profits, sustaining Lederle's position as one among the giants like Merck and Hoffman-LaRouche.

It was a new experience for him. At Harvard his world was his lab, and the labyrinth of his brain, where ideas flashed and teased and beckoned. He could give himself to their blandishments, in self-indulgent, but creative isolation. This ivory tower life was now replaced by the pugnacious, profit-based demands of industrial enterprise.

SubbaRow could make the shift without undue discomfort. For, William Bell and Wilbur Malcolm, the powers-that-be at Lederle, were men with whom he had good rapport. Each had solid respect for the other's talents, aims and objectives. Areas of cooperation could and did develop among them. Lederle became their common cause, their common object of promotion, and care.

There were roadblocks, of course, in SubbaRow's programme of working out alternative processes of synthesising vitamins. The most stubborn of these were the patents held by the devisers of the earlier processes. They could sue all subsequent synthesisers for infringement of patented processes. In his efforts to steer clear of such established processes, he came alive in the round to the problem of patent protection. The infringement suits were real nuisances, tricks of the trade that had come up in the cut-throat competitions for patent procurement. They were filed after slight modifications in the processes that were still pending in the Patent Office. SubbaRow had to be on guard against these attacks from the rear. He had to get savvy about the culture of patent protection.

He learnt the ropes. But he did not learn them at the cost of his integrity. Apart from his salary he derived no side benefits. No slush money ever made its way to him. His inherent distaste for having the spotlight on himself served as a natural preventive against illegal gains and the exposures writ in them. Under patent procedure, the patent is issued in the name of the inventor, even though the company is assigned it. The very word 'inventor' was alien to SubbaRow's make up, and to his perspective on science. For him, there could be only discoveries in medical science, no inventions. All the inventions possible had already been made by nature: man's role could only be to unearth and unravel them. He could never, thus, put down his own name as inventor in patent application forms.

Above all, he did not think scientific ideas culminating in inventions were one-man jobs. No idea was of fixed parentage, he said. An idea could come as a vague perception to one man, develop face, physique and physiognomy in the interactions of several minds, several visions at work on the reach and implication of the idea.

This belief in the multi-pronged origin of ideas was one of the reasons why he could not succeed in synthesizing thiamine. Thiamine was a cure for beriberi, prevalent in Andhra, his home state. There was a wide and growing market for it in the USA too, where it was used for the enrichment of bread and cereal.

Could he synthesise the vitamin for Lederle?

The usual patent hassles were there. Merck and Hoffman-LaRouche held all the patents for the processes developed by scientists from Columbia University. SubbaRow developed his own process, which was partly covered by Hoffman– LaRouche patents. He tried, without success, to persuade the company to allow him the use of their patent. He resorted, thereupon, to perfecting a process developed by an English duo, Todd and Begel. It was believed to be unpatented. But Hoffman-LaRouche managed evidence proving that their own scientists had worked out the process one day before the British group, and so got the patent.

This was when a New York company offered to sell to SubbaRow the services of a chemist in their employ, who had worked with the thiamine group of Merck. Any processes resulting from this chemist's work at Lederle, was to be patented for the New York company at Lederle's expense. Lederle, in return, could obtain an exclusive licence from the company at five per cent royalty.

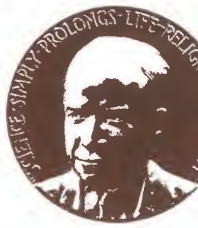
SubbaRow understood and allowed for financial conditions. But he could not understand how ideas and brain work could be divided as so and so's and not so and so's. Half of the ideas of Lederle's men and their foundations were derived before they began work here, and Mr. X's ideas themselves originated while he was working on B_1 (thiamine) at Merck, he said.

Thiamine was, thus, lost to Lederle. Other losses, partial or total were there too, though not for reasons connected with scruples. They resulted from either manufacturing problems or due to failure in synthesis. Among the latter were Inositol, Choline and Para-amino-benzoic acid. Riboflavin,

on the other hand, was a victim to manufacturing problems. The fermentation tanks for storing and precipitating the vitamin were faulty and the fermentation broth got contaminated. When this was set right, the iron pipes connecting the tanks were found to destroy twenty per cent of the riboflavin because they were not glass-lined. A re-piping job was undertaken, which put up the total cost of the plant to three hundred thousand dollars. In between, several gallons of the broth went down the drain due to a mistake of the operators who were not familiar with the piping system. By mid-1944, however, Lederle was making 75 kilos of riboflavin per week. But the price fell and riboflovin manufacture became unprofitable. The patents he got the company in the first three years of his work there were impressive. Lederle was producing, by mid-1944, calcium pantothenate, riboflavin, pyridoxine and biotin although not with good profits.

They were years of quiet content at achievements made, and calm acceptance of failures reaped. The three men made a good team – William Bell as President and the provider of funds, Malcolm as Director of Laboratories and the organiser of facilities, and SubbaRow as Director of Research, the idea man.

It was a good feeling to have, a good state to be in for the leap forward in pharmaceutical work that he was soon to make.



Closing In On The Killer of His Brother

Nestor Bohonos, biochemist who acted as SubbaRow's problem solver on vitamin and antibiotic projects. (Photo: S P K Gupta)

For a long time SubbaRow went along with the belief prevalent then that tropical sprue and pernicious anaemia were the same, requiring similar treatment. He naturally thought for a long time that Fraction I spelt the revenge for the deaths of his brothers Purushottam and Krishnamurti that he had been thirsting for.

He came alive to the different natures of the two diseases after two Bombay doctors at the Haffkine Institute— Dr. Lucy Wills and Dr. Manek M. Mehta – established it by a study of expectant mother in the city. The women were from the poorer strata. Their digestive systems were sound. But during pregnancy or during illness their blood was affected by the chronic nutritional deficiency of their diet, and they contracted sprue. But the pernicious anaemia patients of Boston had degenerate stomach walls and they could not digest their blood-building rich food. Dr. Wills also reported that sprue in monkeys was cured not by APAF-rich liver concentrates, but by crude liver extracts.

But then in stark contrast a sprue patient of Jacobson got better with an APAF-rich liver

Seven of the folic acid team with Coy Waller, who solved the last of the synthetic problems, holding the first jar of the synthetic vitamin. (Photo: Lederle)

extract. SubbaRow neither doubted Lucy Wills nor welcomed Jacobson's findings. He simply set about testing every fraction he extracted from liver on both sprue and pernicious anaemia patients. Sprue is not common in the US. So he set up a sprue investigation programme in Puerto Rico, under Dr. Ramon M. Suarez. Liver extracts, when pronounced beneficial by Suarez, were concentrated for the sprue factor by SubbaRow's men at Pearl River. This went on for two years. And at the end of it they found that what they'd harvested were known vitamins of the B Complex. The sprue factor had simply got lost in the concentration process.

But it was victory that he held in his hands, not defeat: victory as yet unknown to him, even though it was to prove expensive and unworkable in the end. He was testing a liver fraction for a chick growth promoter and this turned out to be the sprue factor. It came to be known as folic acid later. The man who had tracked the chick growth factor in yeast was E.L.R Stokstad, of Petaluma, California, and SubbaRow had him over for the concentration of the factor that was found to be doing double duty by promoting chicken growth and curing sprue. His chances of success were bright. Finance was no problem, for the Lederle umbrella stood high and wide. Both liver and yeast could be bought in unlimited quantities. His pilot plants could process a thousand pounds at a time. Two friendly microbes which thrived on the factor supplied clues for concentration. And above all, there were rich human inputs of sensitive expertise coming from SubbaRow, and unsullied, youthful zeal coupled with professional skill coming from Stokstad.

They tried first a tar-like waste from pork liver. Stokstad's task was to concentrate the

SubbaRow with four others of the folic acid synthetic team. (Photo: Lederle, courtesy: J H Boothe)

product to the extent necessary for obtaining folic acid of standard potency — one million units per milligram. The potency that SubbaRow had got before he put Stokstad on the job was 20 units per mg. Stokstad, in other words, was to increase the concentration 50,000 times over!

Step by step, Stokstad went ahead with his task of increasing concentration. Helped by SubbaRow's thorough grounding in organic chemistry, he began by obtaining 340 units per mg from alcoholic ammonium extracts taken from liver waste. This represented a 17 fold increase in concentration. It went up to 420 units, a rather meagre rise. But later, with a new technique called chromatography, which was an improvement on the charcoal adsorption technique of agonising slowness that SubbaRow had used in his Harvard days, the concentration went up to 3450 units, 170 times more. There was still a long way to go. But chromatography saw him through. He got to 370,000 units per mg. Then to 660,000 units. And then, finally, on January 11, 1943, one year and three months after coming over to Pearl River to join SubbaRow, Stokstad produced a yellow gelatinous mass which was the pure methyl ester of folic acid. It had an activity of 1,030,000 units per mg. obtained in quantities of one-eighth of a milligram per kilogram of liver. This worked out to 454 kilos of liver, costing 255 dollar, yielding 60 milligrams of folic acid, the size of a pea! It was simply not an economic proposition.

The liver approach, accordingly, had to be abandoned. And with it some 100,000 dollars were written off along with more than a year's dedicated work by Stokstad.

But it was not just money that led to the jettisoning of the liver programme.

For one thing, Parke, Davis had announced in *Science* — about the time that Stokstad was engaged in crystallising folic acid, the last stage in folic production — that their scientists under J J Pfiffner had isolated crystalline folic acid from liver. Three weeks later Merck reported that they had isolated a growth factor akin to folic acid. Stokstad by then had obtained 'bladed crystals' of folic acid. But SubbaRow was not too keen on entering into competition with Merck and Parke, Davis. More important, he had already made considerable headway in folic isolation from folic-rich fermentation broths. This, more than the financial drain, was the reason for the switch over. These fermentation broths had been prepared from the folic acid producing *Corynebacterium* of the lactic acid class of bacteria.

It was discovered quite by chance.

SubbaRow was walking over to the laboratory one afternoon in 1942 with a colleague

Child with anaemia: Folic acid and vitamin B_{12} reduce the need for blood transfusion. (Photo: World Health)

carrying a tray of culture flasks of the fungus *Eremothecium ashbyii* or *E. ashbyii*. The fungus helped in increasing riboflavin yields. With SubbaRow was Henry Piersma, in charge of the riboflavin programme. Purely on impulse, one of them, either SubbaRow or Piersma, wondered if the culture of *E ashbyii*, so rich in riboflavin, wasn't producing any other vitamin. Why not have the sample of the culture analysed?

They did.

And the sample was chock full of folic acid.

Things moved fast now. Dr Brian Hutchings, biochemist from the University of Wisconsin, developed a medium for the microbe to grow quickly. The fermentation experts got together and grew the microbe in large, 100 to 200 gallon, tanks. They prepared fermentation broths in large batches for Hutchings to work on. Using the methods that Stokstad had used to isolate folic acid from liver waste, Hutchings worked on the broths and successfully isolated folic acid. But crystallisation proved a problem. After more than a year of vain attempts, Nestor Bohonos, working on another project, was brought in to assist Hutchings. Their joint efforts met with success and in August, within two months of Bohonos coming in, Hutchings was able to obtain uniform folic crystals.

This was when SubbaRow dropped liver waste for fermentation broths. Efforts for higher yields were set in motion. Two glass-lined kettles of 1,000 gallons each were ordered for expanding the pilot plant. A year later, in 1944, however, SubbaRow had to face the bitter truth that the fermentation process had not taken off. Amidst caustic comments by a Lederle vice president that a river of broth would be required to produce folic acid of a noticeable quantity, SubbaRow made fresh attempts by reorganising his research along more production-oriented lines.

Assisted by S.H. Babcock Jr. and George Hayes, SubbaRow was able to produce about 15 grams of folic acid per week at an estimated cost of two hundred dollars a gram. Hopes ran high in January 1945 that costs would be brought down to four dollars a gram. Fermentation was started in large tanks using cheaper ingredients for the fermentation medium. New problems did develop. But these were solved.

However, on August 23, SubbaRow told the fermentation group to wind up its operation, close shop. Folic acid had been synthesised by his organic chemists!

How had this happened?

Simply due to the fact that SubbaRow never made a fetish of any one approach to a problem. He started with the premise that more than one approach always existed for the solution to any problem. And he often had them all going simultaneously. Simultaneously with switching over to fermentation broths from liver waste, thus, he initiated studies for synthesis. And the abandoning of the liver waste method, as we have seen, entailed brushing aside all the painstaking and very promising research that Stokstad had put in, not to speak of the 100,000 dollars that had gone into the work already. Chemical studies

A pregnant woman: She would be wise to take folic acid regularly to protect the foetus against abnormalities. (Source: Internet)

for the synthesis of folic acid had been thus initiated in August 1943 along with the fermentation broth method.

It was no straight and simple route to success yet. Gustaf Carlson, his top organic chemist, left Lederle. This sent Malcolm into a panic, what with stiff competition from Parke, Davis, and Merck hard at work on synthesis. He wanted Vincent Du Vigneaud of Cornell University brought in. But SubbaRow wanted no big shot throwing his weight around and taking over the project. He wanted no replacement for Carlson. He would supervise the work himself.

He began, along with Stokstad and Hutchings, breaking down the folic molecule to understand its structure. They found, firstly, that glutamic acid, from which gluten, the wheat protein, is built up, was one of the constituents. Another was a fluorescent pigment akin to xanthopterin, which is the yellow colour of butterfly wings.

The pterin group of compounds have a 'pteridine' nucleus. The researchers' job was to identity this nucleus. SubbaRow brought in two more members, John Mowat and Jim Boothe, to the existing team of Stokstad and Hutchings. But the identification job proved elusive and arduous.

They had better luck with the non-pteridine segment of the folic molecule. By removing the pteridine segment, and dissolving the non-pteridine fraction in sulphuric acid for 16 hours at 100 degrees, they found it had glutamic acid and para-amino-benzoic-acid or PABA. They were also able to figure out how the two were linked, and were able to prepare a compound of glutamic acid and PABA, namely, PABG or paraaminobenzoylglutamic acid. But how was this non-pteridine or PABG segment of the molecule linked to the pteridine segment? At what point of the pteridine nucleus? Was it linked to one or two pteridines? The questions were many, and the answers far off as ever.

They decided, however, to take a chance with the available data, and begin the work of synthesis. By the beginning of 1945, they had some nine different approaches to synthesis. They would try out each, one by one. 'Failure is not of God but of man,' SubbaRow said to his team.

Theoretically to get folic acid, PABG, and TA (triamine), used to synthesise xanthopterin, have to be reacted with a third chemical. The third chemical was to a) react with TA at the appropriate position, b) take on PABG at the right place, and c) provide the hypothetical fourth carbon fragment of which evidence had been got by Hutchings and Stokstad in their breakdown efforts. Their hypothesis was to be proved wrong later. But not before more trials and errors had been made.

Mowat was given the task of selecting the third chemical and formulating the approach to synthesis. He opted for Di-Bromo-Propion-aldehyde. The actual task of preparing the aldehyde and making the first attempt at synthesis, however,

Dr William B. Castle tested folic acid in pernicious anaemia patients at the Boston City Hospital. (Photo: S P K Gupta)

Foetus: Folic acid helps ensure the healthy growth of the child in the womb. (Photo: World Health)

fell to Coy Webster Waller just brought in by SubbaRow. Waller's first attempt resulted in a substance that looked like brown mud.

He next tried replacing the aldehyde with mucobromic acid. It had some similarities with the DBP-aldehyde. And it could, he thought, provide the postulated fourth carbon in folic acid. For mucobromic acid was a four-carbon reagent.

Waller got a crude with a folic activity of 0.1%. It didn't exactly enthuse the others. 0.1% was hardly a figure to get excited about. But Waller was sure that it meant something. Was there an intermediary compound that was formed in the process of reacting mucobromic acid with PABG? And did this intermediary compound become folic acid, before decomposing in the reaction process, by combining with TA? If this was so, the only thing to do was to throw all the three chemicals together, let them stew, and see what happened. He asked SubbaRow if he should try this. SubbaRow said, "Coy, try anything. Just get it".

Waller went ahead with his recipe and cooked his chemicals. He got a black gummy stuff. He just couldn't bring himself to take the vile looking thing to the assayists for testing. But SubbaRow sent him on. He was never one to go by looks.

The gummy stuff had one to two per cent folic activity, the assayists reported.

The 'shot gun reaction', as Waller's procedure came to be called, had done the job!

But mucobromic acid was not a good reagent. Carbon dioxide escaped during the reaction. There was thus, no fourth carbon in folic acid as postulated by Hutchings and Stockstad. This meant that not a four-carbon reagent, but a three-carbon aldehyde was the need. The obvious answer was the brown mud lying in Waller's shelf since last July. He had it assayed. And sure enough it had 0.75% activity! The thing to do was to use the three-carbon aldehyde originally chosen by Mowat and throw it along with PABG and Triamine in the shot-gun reaction. The resulting produce had 15% folic activity and a subsequent batch showed 20% activity!

On March 14, 1945, SubbaRow telephoned the good news to the chemists of Lederle's sister units. Bell put them all on a special alert with a memo to 'make haste for the prize is great' and join forces with SubbaRow's team. Within a week, on March 20, that is, the first laboratory batch of 15% pure folic acid material was prepared by the chemists of Calco unit at Bound Brook according to the 'shot gun procedure' of Waller. It went up to 20% on July 6, and finally 3.4 kilos of pure folic acid was ready with the fourth batch on August 3. The entire team drove over in SubbaRow's car to Bound Brook and came back, their heads up in the clouds, with the kilo of folic acid all in one bottle that they had been given.

Regular manufacture began on September 26, about a month after the formal announcement in *Science* on August 31, 1945. The cost of

manufacture was 1.12 dollars for 25 tablets of 5 mgs each. This meant that one gram of synthetic folic acid cost 8.70 dollars compared to 12 3 dollars per gram of fermentation folic acid and 4250 dollars per gram of liver folic acid. The project had cost of a million dollars. Bell was beside himself with joy. He could hardly wait for initiating patent application procedures.

And SubbaRow, expectedly, was at his grumpy, reluctant best. When the time came to put down the list of names on the paper to be sent to *Science* journal for announcing the synthesis, he said, 'Put my name down last.'

But the names were to go in alphabetical order, Hutchings was firm, and thereby he saved grumpy old Suby from the backbench where he was ever ready to place himself.

Amidst the elation of success, somebody in the team came up with the baffling but pertinent question, why should the product have the suffix acid attached to its name? An acid is corrosive, stands in the popular mind for pain and burning. Need it be retained? Wouldn't it inhibit sales? The term 'folic' too was not exactly apt. For it had been derived from 'folium' or the leaves of spinach from where a biochemical research team in Texas had got it. The association of leaves and leafy medication products was strong for SubbaRow. For it was with these green remedies that he himself had been cured by the Ayurvedic doctor Lakshmi Pathi when he came down with sprue way back in his teens. The event and the experience, one might recall, had made him something of an Ayurveda buff. It had been but a phase, and it had passed, but it could still flare up on occasion.

Spina bifida: the spinal cord has been surgically closed putting back the exposed contents of the spinal canal. Folic acid prevents such birth defects.
(Photo: Wyeth Lederle)

However, the term 'folic' at least had benign overtones unlike the positively raspy tones of 'acid' to lay, non-medical ears, who are in the majority. Indeed, doctors had consistently muffled the word even when it was central to the product concerned. Tom Spies, a vitamin-hunter second only to SubbaRow, a pellagra researcher, and a man who crossed SubbaRow's path more than once, had named the anti-pellagra product, nicotinic acid, Niacin.

SubbaRow and his group had called it 'Lactobacillus casei Factor' in honour of the bacterium that had guided its isolation. No medicine could hit the market with that kind of name, of course. On the list of names was the jawbreaker Aminohydroxy-Pteridyl-Methyl-Amino-Benzoyl Glutamic acid, incredible as it seems. It was 'shortened' to Pteroylglutamic acid by Coy Waller, whose shot-gun method of cooking together all the chemicals of the folic molecule had brought synthesis nearer. But even the most ardent couldn't hold that names like these would make a rapport with the public.

They considered glupteramine next, 'glu' for glutamic acid, 'pter' for pteridine, and amine for para-amino-benzoic acid. But somebody with foresight pointed out that glup was too close to glop, teenage slang for gooey food.

Vitamin M was the next suggestion, vetoed without ado because folic acid belonged to the B Complex group of vitamins, not M! 'Vitopterin' and 'Biopterin' were next on the list, with a slight edge in favour of the first, after it was modified to Viopterin. But it was shot down because it was too close to a trademark name 'Vioptamin' and nobody wanted an infringement lawsuit on their

hands. A list of eight names ending with 'pterin' was circulated but none of it came to anything. The name Folic Acid seemed unshakable. Clinicians had used it in all their papers. The press had given it currency and coinage. A last ditch effort by the Sales Department of Lederle for New Products in favour of Folvite ended up in its name being printed on the labels with a qualification: 'Folvite brand of Folic Acid'. Further, the sales campaign was to stress that folic acid had 'none of the properties usually associated with acids' and was 'a slightly soluble, tasteless, yellow powder'.

But the question SubbaRow had not yet answered conclusively was that folic acid was not the cure for pernicious anaemia too along with tropical sprue.

The two diseases were not the same as he had learnt as far back as the 30s from the studies of Dr Lucy Wills in Bombay. The properties of folic acid were very different from the APAF fractions of liver. In a way folic acid could be considered a contributory factor in the cure of pernicious anaemia. In 1926 when the pernicious anaemia patients of the two Boston physicians, George H. Minot and William P. Murphy, were being fed a hundred grams of broiled liver a day, they were taking in 600 micrograms of folic acid too present in the liver meal. They could not otherwise have assimilated the 60 micrograms of APAF that the meal contained. But soon liver was beginning to be injected, and was not having to be chewed with great punishment to jaw and palate. The problem of APAF assimilation was thus bypassed.

But matters couldn't rest there, of course. Folic Acid was not central to pernicious anaemia cure, even though some clinicians were making spectacular claims for it in pernicious anaemia treatment.

Unconvinced by the claims, SubbaRow turned his attention to the beautiful pink solution he'd had on his shelf since 1941. It was virtual APAF. But its pink colour deterred him from testing it. The colour was the remnant of the Reinecke salt he had used to precipitate the active material from protein-free liver extract, he thought. But its presence surprised him. For he'd used silver nitrate to break down the salt after it had done the precipitation. Reinecke is toxic. He didn't want to risk it on patients. His aim was to clear away the colour and retain the activity. The work on this went on for almost a year till Otto Wieland, the chemist put on the cleansing cum retention job, threw up his hands. Why use Reinecke salt at all if it was so risky?

But folic acid was now proving to be increasing harmful to pernicious anaemia patients. A spate of adverse results was reported from trials. SubbaRow lifted his ban on the pink solution. Its chance came in 1947, on Christmas Eve. Tom Spies from Havana cabled SubbaRow for the red fraction to administer to a pernicious anaemia patient he had. And SubbaRow, the tyrannical workaholic that he was, stalked his isolationist, Otto Wieland, who was happy buying presents for his family, made him go to the lab, get the fraction and fly it out to Spies in Havana. Spies' patient was a 65-year-old woman. She was in a confused state after three months in bed at home. Spies gave her one c.c. of the special liver fraction. She recovered almost at once. The news made Wieland forgive SubbaRow.

Another patient, a woman allergic to liver injections and prostrate for months with pernicious anaemia, was out of bed by the month end after getting one c.c. of the same fraction. This time Wieland more than forgave SubbaRow. On edge, his nerves in a frazzle after months of fruitless work on the fraction to rid it of colour, he breathed a sigh of relief. His toils and tribulations with the exacting, ruthless demands of SubbaRow for un-salting the salt were practically over.

Officially, however, the last word in the isolation of the anti-pernicious-anaemia factor

went to Merck. The April 16 issue of *Science* carried an announcement from them: "A crystalline compound which in microgram quantities has produced positive haematological response in initial tests in patients with Addisonian pernicious anaemia has been isolated from liver."

Merck called this compound B_{12}.

Merck later said that B_{12} was not isolated from liver but from fermentation broths of an antibiotic called grisein. It was known that all but 20 of the 25,000 micrograms of B_{12} present in a ton of beef liver got destroyed by the usual fractionation methods. Fermentation broths, it should be recalled, were the source that SubbaRow and his team had been the first to tap in their search for a cure for sprue. They had conclusively proved that fermentation broths were rich sources of vitamins. All later research, from which B_{12} resulted, were thus in many ways take-offs from this milestone that SubbaRow had laid.

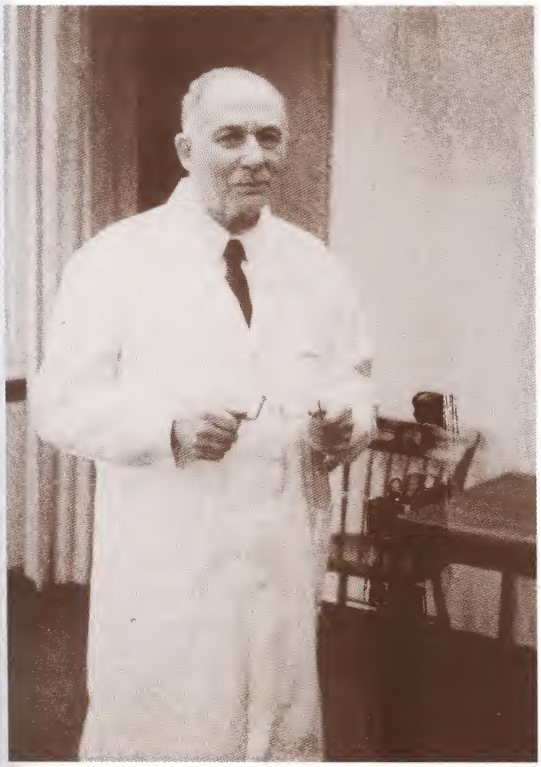
The relevance of folic acid and its areas of applicability have spread in many directions since SubbaRow's death. WHO and UNICEF have collected extensive data on the relationship between nutrients and mental functioning. Their findings have led to the inclusion of folic acid and Vitamin B_{12} among the 'smart' nutrients. Folic acid deficiency causes fatigue, depression, difficulty in concentration, lower general intellectual functioning and memory. And Vitamin B_{12} deficiency is associated with poor intellectual outcome, emotional distress and memory dysfunction.

In addition, folic acid has been found since SubbaRow's time to ward off spinal cord defects in newborns. The US government, accordingly, has required that all flour, pasta and other grain products manufactured after January I, 1998, be enriched with the this vitamin. By mid-1999 this had already reduced homocysteine levels in cross sections of the US population. Homocysteine is suspected to be among the causes of heart disease,

Heart Patient: Killer heart and brain episodes can be significantly reduced if folic acid's ability to reduce homocysteine levels in blood is confirmed. (Photo: World Health)

and among the risk factors. A patient of homocysteinurea, a rare genetic disorder, usually dies of heart attack or stroke by the age of 20. Folic acid has been found to be beneficial in controlling this condition, thereby giving hope to heart patients.

The Folic Aftermath: Crusade Against Cancer



Sidney Farber was the first to demonstrate the role of SubbaRow's antifolics in the fight against cancer by effecting remissions in children suffering from acute leukaemia. (Photo: S P K Gupta)

Folic acid proved to have a reach far beyond sprue. It seemed set to take on cancer. SubbaRow had had a hunch that it could do this ever since a report from the Mount Sinai Hospital at New York that it inhibited the growth of cancer cells in mice. This was in 1944, the year in which he set off on his track of Aureomycin. The two lines of research were running on parallel tracks.

The tests at Mount Sinai Hospital, conducted on mice and rats by Dr. Richard Lewisohn, were exciting and highly promising. Of 89 rodents afflicted with breast cancer, and test-treated with a daily dosage of 5 micrograms of folic acid injected intravenously, 39 had a complete cure.

SubbaRow asked Lewisohn to repeat the tests with both liver and fermentation folic acids. Liver folic was inducive of cancer cell growth. But fermentation folic once again proved effective, curing 40 percent of the mice tested. Lewisohn, who published his findings in *Science* on November 8, 1946, had got his result from teropterin, the fermentation folic. A tremendous public demand for teropterin came up, with requests for supplies from various research groups, even those sceptical

Child recovering from leukaemia: Antifolics devised by SubbaRow effected the first significant remission of acute childhood leukaemia, and opened a new frontier in the fight against cancer. (Photo: World Health)

of the findings. So dreaded was the disease.

SubbaRow agreed to meet the demand. He did do so, after putting in considerable laboratory work to produce the special 3-glutamic compound that was needed for synthesising teropterin. Teropterin became synthetically available by 1947. But SubbaRow also began his own evaluation work with Sidney Farber at Children's Hospital in Boston. Farber and his colleagues from other hospitals were making preparations to study the effects of teropterin when a Dr Max Klainer obtained a supply of teropterin from them for a cancer patient of his, an Armenian woman. Her case was extreme -- practically hopeless with surgery for breast cancer leading to secondary cancer (metastasis) that had affected her spine and ribs. She was put on a combined treatment of hormones and of teropterin, and further surgery to remove her ovaries. Gradually, hormones and pain killers were dropped and only teropterin was given. She was discharged some four and a half months later, on June 5, no more the inert, bed-ridden woman she had been. Within ten days of the teropterin-only treatment she had been able to swing her limbs down the bed. Three days later she had sat up in a wheelchair. A month later she could walk around with a cane. On discharge she was fitted with a back support, and advised just a maintenance dose of teropterin. By December she was fully able to walk around. And she complained of just a mild pain in the lumbar region.

Her case was not really a decisive victory for teropterin because other forms of treatment had also figured. But Farber and his associates decided on further trials on 90 other cancer patients, considered incurable. Their ailments ranged from acute leukaemia to malignant tumours. Within a month 27 patients died, but the post-mortems of 13 showed no ill effects from teropterin. Above all, those alive showed remarkable improvement despite metastasis. More tests were conducted. Were the heartening results of the Boston group under Farber due to the psychological factor of the patients' knowledge that special efforts were being made for them? This was disproved when tests instituted under Dr Louis Wright at New York's Harlem Hospital — tests in which the patients were not told of teropterin or the special treatment it signified — also showed similar heartening results.

The best and most heartening news came from Lewisohn at Mount Sinai Hospital in New York, where Babe Ruth, the legendary baseball player, was admitted with terrific pain. A malignant growth in his neck had robbed him of his faculties of sleeping, eating and talking. Six weeks of intramuscular injections of teropterin put him out of pain and restored the capacities which had deserted him.

The clinical trials, however, heartening as they were, could only establish that teropterin was a palliative.

Crohn's disease of the small bowel is also known as regional enteritis. A similar inflammatory picture may occur in the colon either alone or with small intestine involvement. This form of colitis can be distinguished from ulcerative colitis and is referred to as Crohn's disease of the colon. Clinically these disorders are characterised by recurrent inflammatory involvement of the intestinal segment with diverse clinical manifestations often resulting in a chronic, unpredictable course. Major clinical features are fever, abdominal pain, diarrhoea often without blood, and generalised fatigability. *New England Journal of Medicine* reports that methotrexate may prevent a relapse in sufferers who are in remission.
(from a Textbook of Medicine)

The focus now shifted from folic derivatives to anti-folics or folic antagonisis as likely cancer cures. There were reports from scientists engaged in animal studies, that folic acid encouraged leukaemic cells, and that, therefore, anti-folics could well be tried as inhibiting factors. SubbaRow decided to follow up this suggestion. The first anti-folic that he got prepared, X-methylfolic acid, did not produce definite results. The second, pteroylaspartic acid, also failed in saving its test patient, a four-year-old girl with fast progressing leukaemia, but her bone marrow condition after death showed an improvement not noticed before. Farber, who had done the test, now asked for more powerful folic antagonists. Aminopterin was more than a hundred times stronger than pteroylaspartic acid. It was the most notable of the anti-folics. SubbaRow had it further purified, obtaining greater control over its antagonistic property. Finally, six months after Farber's request, he made it available to him. Aminopterin was also tried by Leo M Meyer of King County's Hospital in Brooklyn, along with Sydney Farber in Boston. Meyer had only deaths to report from his tests on *adult* leukaemic patients. But Farber's experience with leukaemic *children* was different. One of the children was Robert Sandler. He was below five years of age. It was the age most susceptible and most friendly to the brief and ruthless course that is characteristic of the disease. Farber put him on aminopterin. In two months he was walking. His bleeding stopped. His belly shrank as his liver and spleen came down to normal size, and his appetite picked up enormously. Five months later he could do with just the maintenance dosage, half a milligram thrice a week.

It seemed nothing short of a miracle. The Boston *Herald* played it up, showing pictures of Robert after the treatment, indistinguishable from his identical twin, Eliot, who had never had a day's illness. A two-year-old girl had no relapse 43 days after the treatment was stopped. A six-year-old boy returned to school after three weeks.

Leukaemia-victim Robert Sandler in remission with aminopterin and identical twin Elliott who never had a day's sickness in all of his three years.

A child was alive 20 months after diagnosis and treatment.

Farber was making no solid claims for the drug. But the medical world thought that the repeated remissions it was producing were noteworthy. What had been established was that anti-folics or folic acid antagonists were effective in leukaemia. But how had the equally effective action of folic conjugates or folic analogues like teropterin and duopterin come about? How was this to be explained?

There has not been any explanation to this contradiction so far.

The Boston *Herald*, as we have seen, hailed Farber's results as spectacular. But the medical journal *Blood* cautioned against wild optimism. All that aminopterin did, it said, was to put leukaemia under 'temporary control' while conceding that even a temporary remission was an important development in the fight against a killer disease like cancer, and that it could be a watershed in research. Further researches only proved that aminopterin brought about remissions of around four months maximum in leukaemic patients, and that relapses occurred without exception. Continued use depleted the bone marrow, and brought about the degeneration of the alimentary canal. What was needed, experts said, were folic antagonists less toxic and more powerful than aminopterin.

SubbaRow and his team found that the toxic quality of aminopterin could be reduced by manipulating its molecule. The compound that had one-fifth its toxicity was methotrexate. If dosage was increased to five times more than aminopterin, this would match it in power. Both have the same ill effects at comparable dosage levels. But methotrexate allows the physician to adjust the dose to get the best out of the treatment. At the moment it is the preferred drug.

Folic acid antagonists paved the way for the treatment of leukaemia by chemotherapy. Three drugs later came into play here. The anti-folics are one. The second are anti-purines which are the antagonists of purines that are needed, like folic acid, for the synthesis of nucleic acid. The third is 5-fluorouracil, which blocks DNA synthesis. Together the three 'anti-metabolites' set the chemotherapeutic process for leukaemia cure in action. Antibiotics and transfusions are added to restore a near-normal blood picture. However, by cure is meant nothing more than the gift of a five year lease of life to the patient. Chemotherapy, in other words, is a postponement of death. No more. It destroys the normal cells along with the cancer cells and has painful side effects such as diarrhoea, hair loss and nausea. Nonetheless it provides a reprieve from death, which is a blessing not to be dismissed if seen from the point of view of those pitchforked closer than others to the jaws of death.

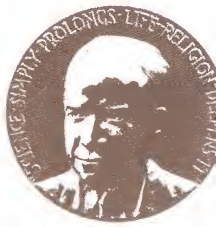
SubbaRow began to chalk out a multi-pronged campaign against cancer based on hypotheses deduced from experimental results of the research groups at Pearl River.

Required for metabolism of normal cells, folic acid was equally essential for cancer cells — especially to get a foothold in the body and flourish — whereas some anti-folics interfered with cancer-cell metabolism. Further, an analogue of aminopterin and methotrexate could serve as a tool to control the amount of folic acid available for tumour growth in animals without depriving them of adequate vitamin for normal growth. When three different types of tumours — Rous chicken sarcoma, mouse 180 sarcoma and Bittner's milk tumour — responded differently to a series of new anti-folics, he surmised that tumours could be classified on the basis of their reaction to chemical compounds. Dr Louis Wright agreed to test SubbaRow's hypothesis at Harlem Hospital.

SubbaRow at the same time set up a cancer screening programme of all the compounds he produced in his laboratory. He also had a theory that a highly nutritive fluid called ascites promoted cancer tumours in animals, and planned to study this phenomenon by inducing ascites in rats. Elated when a member of his team succeeded in the induction efforts, he drew up ambitious programmes for further research.

SubbaRow now put forward a big programme for a new cancer research laboratory. The engineering plans for the laboratory were approved only to be abandoned when SubbaRow died in August 1948. Those who in his lifetime shared his dreams of conquering cancer and later missed his direction say the dreams would have come true had he lived another ten years.

Methotrexate, as noted, has been since SubbaRow's time used by the medical profession not only to fight cancers but to control a range of unconnected illnesses such as rheumatoid arthritis, psoriasis and Crohn's colitis as well as medical abortion in ectopic pregnancy. Most recently has come a report in *Chest* that low-dose methotrexate spares steroid usage in steroid-dependent asthma patients. The SubbaRow lineage, we see thus, continues fertile.




SCIENCE SIMPLY PROLONGS LIFE RELIGION DEEPENS IT


SCIENCE SIMPLY PROLONGS LIFE RELIGION DEEPENS IT
YELLAPRAGADA SUBBAROW
1896-1948
SCIENTIST · TEACHER
PHILOSOPHER ·
HUMANITARIAN
DIRECTOR OF RESEARCH
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY

The Run-up To Panacea : The Golden Dawn Of Antibiotics

Rene Dubos discovered gramicidin and tyrothricin at New York's Rockefeller Institute for Medical Research and owed it to SubbaRow that they became 'the first antibiotics to be produced commercially'. (Source: Internet)

From a chronological point of view, the first antibiotic was discovered in 1940 by Rene J. Dubos of New York's Rockefeller Institute for Medical Research. It was gramicidin. Dubos had spent more than ten years getting the bacillus that destroyed most, though not all, of the pneumonic germs that were breeding in New York's sewers, and threatened the city's population. A Rutgers-trained agricultural bacteriologist, Dubos had been retained by the Rockefeller Institute for the sanitation job.

The name gramicidin was a bit of a joke. Gram stood for the dye that a Danish bacteriologist Hans Christian Gram had developed. It dyed the germs that could be dissolved by a bacillus Dubos had discovered. Those that could not be dissolved by the bacillus, and hence could not be dyed, were gram-negative. The others were gram-positive. Dubos called his antibiotic Gramicidin meaning to honour Gram not realising that the term literally meant the 'Killer of Gram'!

SubbaRow came into the picture at this stage. Dubos's stuff was not pure, as he himself said in his announcement in the *Journal of Biological*

Chemistry. And it was highly toxic: given intra-peritoneally, 0.3 milligrams of it was enough to kill a mouse.

SubbaRow was not put off by its toxicity. He read between the lines of the announcement and saw in it the augury of a new era in antibiotic therapy, signifying the end of the sulpha era. He decided to purify Dubos's material. Along with his collaborator Henry Piersma, he improved on the techniques of preparing the culture broths for the antibiotic. He adapted Dubos's methods to his own methods for purifying liver fractions. Four different procedures resulted from these revised techniques, all of them more productive of gramicidin than Dubos's method.

Dubos himself asked for SubbaRow's product to treat mastitis in cows. For some time, mastitis-affected cows seemed to be a potent area of use for gramicidin. But the tests did not establish this in the final count. Toxicity remained and the animals showed higher fever as well as damage to mammary tissue. The Lederle management, in fact, explored the possibilities of using gramicidin as an insecticide. The anti-mastitis programme in effect had to be abandoned.

Matters stood there till late 1941 when a request for 5 grams of tyrothricin came from Dr. Chester Keefer of the Evans Memorial Hospital of Boston. Tyrothricin was the active material of Dubos that turned out actually to be a mixture of gramicidin and another antibiotic identified as tyrocidine. Keefer said that he had had very encouraging results from local applications of gramicidin on superficial skin infections such as leg ulcers. But results from other cases had not been as encouraging and so he wanted more tests to define the scope of gramicidin. Soon he asked for more supplies. Another request came from Dr. S.J. Crowe of Johns Hopkins who had good results from using gramicidin in post-surgical wounds.

Production was started a second time but a break again occurred because of SubbaRow's preoccupation with other drugs. It was resumed a third time when strong and decisive endorsements of gramicidin applications to surgical wounds came from several medical quarters.

Demands now came from the Red Cross for first aid dressings. Around October 1943, a little over a year after the formal Red Cross demand, SubbaRow and his collaborator Henry Piersma were able to send the consignment.

It was the same with penicillin : refining and purifying the original product of Alexander Fleming. What caught SubbaRow's attention again,

Alexander Fleming was toasted at Waldorf Astoria Banquet on 25 June 1945 by admirers in USA including SubbaRow (second front row table on the right) who would better his penicillin with tetracyclines. (Photo courtesy: Lederle)

as with gramicidin, was an article in a medical journal, this time *The Lancet*. Written by a team of Oxford pathologists, it said that penicillin was remarkably active against organisms responsible for gas gangrene. Alerted, SubbaRow obtained the culture of the penicillin fungus that had been sent for identification, way back in 1930, to Charles Thom of the US Department of Agriculture. It didn't give as much penicillin as Fleming claimed. His own efforts, as SubbaRow said in his report to the management, would be to vary the medium for higher yields. He did succeed. By adding water soluble casein to 2 units of the medium he and Piersma got 20 units per c.c. of culture as against the 2 units by the Oxford Group. His was purer as the Oxford Group itself acknowledged when they came to Pearl River to explore avenues for higher penicillin production.

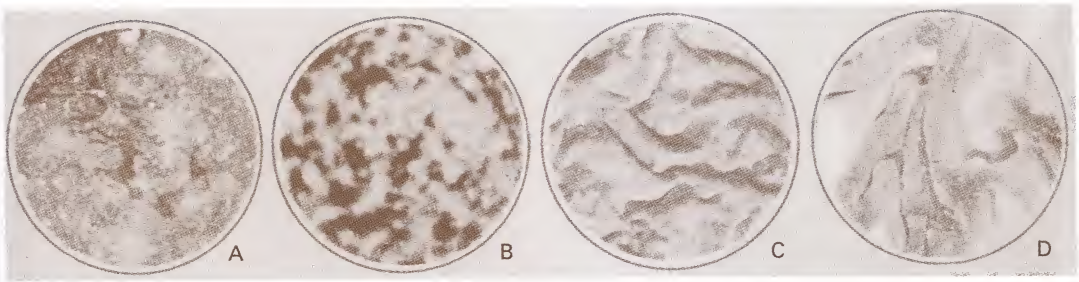
Higher production — not surprisingly — was the interest of many other pharmaceutical houses in addition to Lederle. Many more from the parent series *Penicillium notatum* had been developed and made productive. Also the co-operation of the big companies was being sought by the U.S. Committee on Medical Research (CMR). Lederle was represented by SubbaRow at the conference called by CMR Lederle did not have the facilities for the yield — a kilo — that was being demanded by CMR for trials. Nor did the other companies have the facilities. But they were making tall claims in a spirit of business bombast. SubbaRow was just not the man for tall talk. He and his co-workers thought that chemical synthesis was the only way for the needs of the military that CMR was trying to meet. The big, boasting companies also thought so. Chemical synthesis work got started accordingly at Lederle Laboratories. They were given up for lack of results. But the effort did get Lederle into the penicillin programme of the War Production Board in 1944.

Here again, Lederle was downgraded and was assigned production in two-quart milk bottles by the surface-culture process. It was a bitter pill to swallow for the management even though the Board's assessment of Lederle's capacity was fair. Hurt pride was not restored till 1946, one year after the war, when the management built a deep tank plant with a capacity of 1.5 million vials of penicillin a month.

SubbaRow oversaw the construction and working of the plant. And in just a few months Lederle's penicillin sales were a multi-million dollar business.

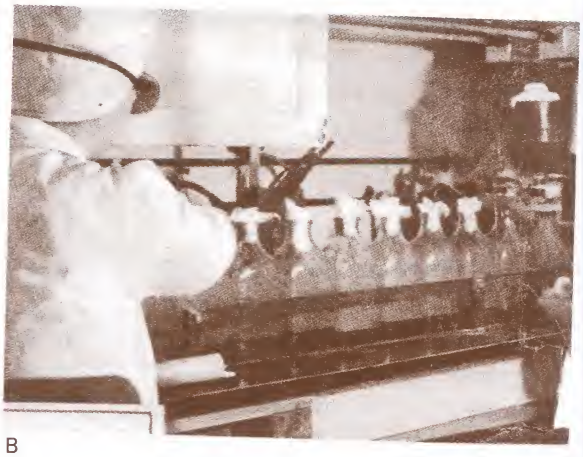
Dabbling with gramicidin and penicillin at the dawn of the antibiotic era was valuable experience for SubbaRow when he decided to start a programme to find an antibiotic of his own that would have a broader range against bacterial diseases, an antibiotic in fact that would be a panacea, a cure-all, for fevers of any kind.

That is a story that requires telling all by itself.



Penicilium notatum grows in SubbaRow's Pearl River laboratory petri dishes: Spore carriers appear on day 1 (A), white cottony patches form on day 2 (B), amber traces of penicillin in crevices of white mat on day 4 (C), and the antibiotic is ready for harvest of liquid beneath, day 7 (D) mat with heavy golden droplets as the mould reaches peak growth. N.G. Heatley, associate of Fleming, visiting Pearl River in 1941, found SubbaRow's penicillin 'more potent' than the antibiotic produced by the discoverer's group in Oxford. (Credit for photos: Sunday Mirror Magazine, July 23, 1944; Courtesy: Lederle)

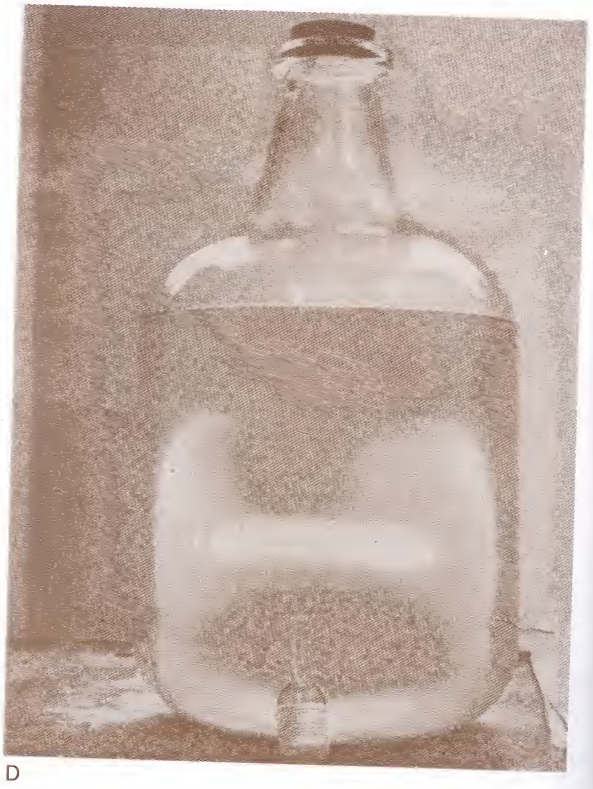
A



B

Penicillin under production in SubbaRow's Lederle Laboratories: A 500-gallon vat with mash in which the penicillin mould is grown (A); the miracle mould is incubated in bottles (B); the vacuum dryer bristling with vials extracts moisture (C); and 16 litres of finished liquid are enough for filling dry penicillin in 3200 vials like the tiny bottle shown with the jug (D). (Credit: Sunday Mirror Magazine, July 23, 1944; Courtesy: Lederle)

C



D

Dress Rehearsal: The Fight Against Filariasis

Filarial worm : causes one of the most disfiguring diseases by clogging lymph ducts and causing lymph to flow into and distorted growth of muscles and other connective tissue. Hetrazan effectively kills the worm. (Photo: WHO)

But before this grand finale, SubbaRow had a lesser but no less significant battle to wage and finish: his battle against filariasis. It seemed only a partial success for a long time, but was found to be a resounding success some 50 years after his death!

Filariasis brings about a living death for the victim. It is rarely fatal but is so distorting physically as to incapacitate movement and disfigure the body abominably. SubbaRow had seen it at close quarters in his hometown, and been appalled by the sight. During his stint in the Madras Ayurvedic College he had frequently thought about the social and the physical disabilities it caused. A fresh and urgent immediacy to the phenomena of tropical diseases came about in the forties because of American engagement in the Pacific war theatre. The soldiers were exposed at close range to these diseases. And on their return they could well infect the civilian population. This dreadful prospect secured a quick clearance to SubbaRow's anti-filariasis programme.

A problem with filariasis is that it operates at two levels in the human body. The first level is

that of the peripheral circulation system where the young larvae, discharged into the blood stream by the adult worm, float up at specific hours of the day and night. The mosquito sucks them in and injects them back after they have matured. This is where the second phase of the disease gets established. The re-injected adult worms sink down to the lymph ducts and gather in the lymph glands. The blocked lymph flows into connective tissue and makes it swell till the affected part bloats up into disfiguring proportions. An anti-filariasis drug thus has to perform the two fold task of killing the larvae, as well as the adult worm. The drugs in use for over twenty years till then were heavy metallic compounds like antimonials and arsenicals given by injection. These were of doubtful use when given over long periods and secondly, they acted only against the adult worms not the larvae. SubbaRow wanted an oral compound that would kill both the adult worm and the larvae. An elaborate screening programme was set up for testing every chemical that was made or was available in the Lederle Laboratories. Five hundred and seventeen compounds were tested. The 180th of them received from Calco was found the most promising. 180-C, as the Calco compound was called, was a derivative of the chemical Piperazine. Further tests of the compound confirmed the findings of the earlier tests. 180-C injected directly into the peritoneum or given orally brought about a rapid fall of filarial larvae in the peripheral blood of cotton rats. It also established that piperazine was the best balance between toxicity and activity. But 180-C was not effective against the adult worm. A more active drug, therefore, had to be found. Under SubbaRow's direction the experiments centred round replacing by other chemical groups the carbethoxy side chain hooked to the nucleus of the compound.

The first compound, got from using a single ethyl radical as replacement, was inactive. To SubbaRow and to none else of his team came the idea of using two ethyl fractions. The worm went into death spasms. The two-ethyl compound was called 84-L because it was the 84th compound from the Lederle Laboratories to be tested. 84-L was tried on over 200 cotton rats and some 25 dogs. Reductions of filarial worms in cotton rats only occurred after several weeks of administration and the effect on the adult worm was even less remarkable. Dogs were usually demanded back by the owners after treatment. But in the dogs on which autopsies could be performed, the hearts, where the filarial heartworm collects, were found to be clear. The dead worms were located at the terminal branches of the pulmonary artery.

Woman with elephantiasis: After years of hesitation in employing it in mass campaigns, WHO has cleared Hetrazan for employment on a mass scale in filariasis endemic areas. The unpleasant side effects previously encountered are attributed to unnecessarily high dosages prescribed. (Photo: WHO)

Clinical trials were felt to be in order now. Six members of the 84-L team took the drug themselves, a high dosage of 8 mgs per kilo of

Hetrazan: WHO has determined that a single dose of DEC, given concurrently with Ivermectin, is enough to keep blood free of filarial worms for a whole year. (Computer-generated by Ravi Narain)

body weight. None of them reported anything worse than nausea. Equipped with these endorsements, SubbaRow launched the clinical trials early in 1947. He chose Puerto Rico the American-administered Caribbean Island for the tests. Twenty-six Puerto Ricans were given the drug orally. Blood stream larvae as well as adult worms from the lymph disappeared rapidly and no toxic reactions were recorded. The tests were extended to orphanages and asylums where longer periods of observations were possible.

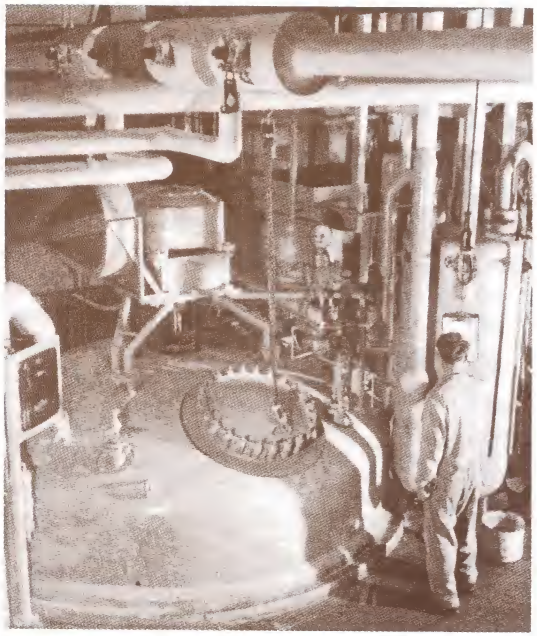
In late 1947, Redginal Hewitt of SubbaRow's team formally presented Hetrazan, as 84-L was christened, at a conference of the New York Academy of Science on the chemotherapy of filariasis. Hetrazan was given extensive trials in 1951, three years after SubbaRow's death. St Croix in the Virgin Islands was among the places where tests were made. The other places were Guatemala, East Africa, India and Tahiti. Eighty-five per cent of the people in St Croix, which was an endemically affected area, were found free of larvae a year later. More extensive and ambitious tests were carried out in 12 states in India from 1955 to 1959. The tests ran the full five-day course.

The results were not one hundred per cent favourable, from the official point of view. The Indian Council of Medical Research ruled that the side reactions were undesirable and a more non-toxic filaricide had to be discovered for a chemotherapeutic approach to the disease.

The side reactions which caused the strictures to be passed against Hetrazan consisted of nausea and stomach upsets, fever and body ache. But these are caused by the sudden release of proteins into the body by the destruction of the larvae. They are, therefore, evidence of the curative process rather than of toxicity.

Todate, 84-L has not been improved upon by any other less toxic drug. Physicians have tried such pretenders as Ivermectin but journeyed back to Hetrazan as the primary tool for the control of lymphatic filariasis. It has even been cleared for mass campaigns against the scourge of elephantiasis. Giving its clearance for this, the World Health Organisation says its unpleasant side effects were due to unnecessarily high dosages previously prescribed. It was enough to administer a single dose of Hetrazan, better known now by its generic name *Diethylcarbamazine* (DEC), concurrently with Ivermectin, to keep the blood free of filarial worms for a whole year. DEC has become the key element in WHO's global campaign for the elimination of filariasis.

Panacea



After production problems were solved by Joe Niedercorn, Charles Pidacks and George Krupka under SubbaRow's close supervision, the aureomycin mould began to be grown in tanks. (Credit: Lederle)

SubbaRow, as we have seen, had a healthy scorn for precedents and conventions when it came to charting further courses of scientific investigation. He was never one to set much store by the degrees a scientist had got. He never equated innate capacity with the scrolls of paper that a candidate possessed.

When the urge to search for antibiotics came upon him, therefore, he decided to steer clear of a) experts, and b) ex-non-experts threatening to become neo-experts once settled in their niches. Above all, he steered clear of universities and the material facilities they boasted of. His own laboratory was to be his cockpit as well as workshop. The greatest of his discoveries, the world's first broad spectrum antibiotic, Aureomycin, to come two years and eleven months after his synthesis of folic acid in August 1945, was the fruit of sweat poured in the confines of his lab at Pearl River. He wanted now contiguity of work and work-site. No benefice or bounty of university, hospital or industry was to disturb this arrangement he sought for his pursuits.

Lederle chief, William Bell, was filled with misgivings at his research director's extreme

After many a heartbreak in getting pure, crystalline Aureomycin out of the broth fermented in tanks, the moisture in the antibiotic was removed in these vacuum driers. (Credit: Lederle)

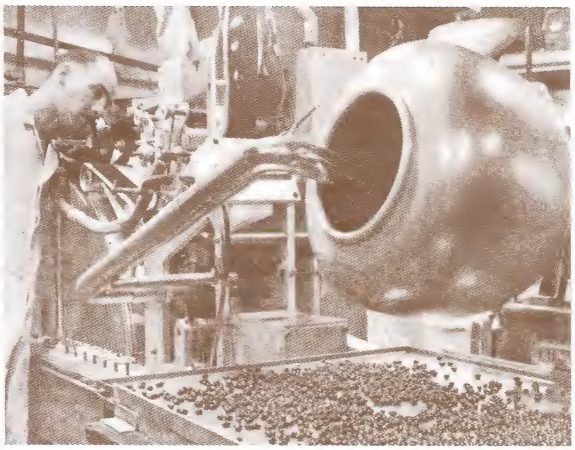
stand-offish attitude. But SubbaRow overrode his chief. With audacity he broke the connections between professional qualifications and job appointments. He brought in Benjamin Minge Duggar, past seventy and a retired plant physiologist of Wisconsin University, to screen microbes and actinomycetes. He had Joseph G. Niedercorn, leather technologist, for fermentation work. And he had Charles Pidacks, a B.S in organic chemistry, for isolating antibiotics from the fermentation fluids of Niedercorn. Each man working on the Aureomycin project — or A-377 as it was called before its formal christening — was swayed by SubbaRow's supreme ideology of fighting human pain. Each agreed to diversify his innate scientific aptitudes into spheres outside his specialty.

SubbaRow began by an extensive screening of actinomycetes. These are organisms most similar to bacteria in size, and to fungus in structure. And most important of all they are rich sources of antibiotics. The screening of these organisms was Duggar's assignment. Duggar was methodical, untiring in his work and, to the delight of SubbaRow, possessed of an organised mind. He kept himself in close touch with his protégé's investigations. And he learnt that actinomycetes grew in mature, undisturbed soil such as grasslands and pastures. They did not grow in the sewage polluted brooks and ponds that Bell had taunted SubbaRow to go sloshing in as breeding grounds par excellence of antibiotics.

Soil samples from all over the US were accordingly sent for by Duggar and his associates. They were screened for bacteria along with actinomycetes. The products isolated were labelled A for actinomycetes and B for bacteria. The breakthrough came with the 71st bacterial isolate B-71. It was identified as *Bacillus polymyxa* used in the manufacture of synthetic rubber. Crude broths from its cultures protected chicks from fowl cholera caused by gram-negative bacteria. These bacteria were generally beyond the reach of penicillin and the other antibiotics then known.

This was an exciting development, and it called for full-scale follow up work.

He straightway set up his polymyxa team headed by John N. Porter, mycologist, brought



Aureomycin being capsuled after it was found that it was effective orally; it was the first antibiotic that did not require to be administered by injection. (Credit: Lederle)

from Harvard. The team isolated a variety of strains of B-71 from 65 samples brought from 22 states. The strains varied in their capacities to produce the antibiotic on varying culture media. Eighteen were finally chosen for comprehensive tests as they had proved effective against fowl cholera in chicks. None of them was better than B-71. It was, therefore, chosen for chemical isolation. The work of production and fermentation proceeded from 20-litre bottles to fifty-gallon and finally to 200-gallon tanks. Eventually, from a corn steep broth, Porter and his team crystallised the antibiotic, reaping 21 percent of the tank's antibiotic activity.

SubbaRow sent the drug to Dr. Perrin Long of Johns Hopkins Hospital for testing. Long found it more potent than streptomycin against gram-negative bacteria. But it was more toxic when administered to Swiss mice. Long weighed the pros and cons—and went in for human tests. His first patient was a nine-year-old boy critically ill with a skin eruption and a fatal side infection. Both conditions were unresponsive to penicillin and streptomycin. Long injected B-71 under the skin. The eruptions cleared on the third day. The boy was sent back home on the 8th day. Long also reported cures in cases of whooping cough, blood poisoning, meningitis and undulant fever. He wanted now to send the antibiotic to India for bubonic plague; but SubbaRow had developed misgivings about the drug. It caused kidney disorders if injected directly into the bloodstream. He wanted Long, instead, to test a new antibiotic that Duggar had isolated. It was safer and was effective against both gram-negative and gram-positive bacteria.

Benjamin Duggar, authority on fungus research, whom SubbaRow employed on antibiotic screening which yielded Aureomycin. (Photo: Lederle)

The antibiotic was golden yellow in colour. Its sunlight colour gave it the name by which it was to be known eventually: Aureomycin from Aureus, the Latin for golden.

Duggar had extracted the mould from 12 soil samples sent by an old friend. It was the 67th sample in that batch of twelve, from 61 to 72, and the 377th since the search for actinomycetes began. Duggar poured out the twelve samples into isolation plates on August 20, 1945. In around a week's time, colonies of actinomycetes appeared in the agar medium. These were transferred to test tubes. The tubes were maintained at a temperature of 28 degrees. After another week the isolate 377 or A-377 began to grow spores. Duggar took out a few spores from the tube, put them in the centre of an agar plate, and let them grow. On September 20, exactly one month after he began his tests on the batch of 12, Duggar took out a little of the culture broth from four test tubes in which deadly disease germs had been grown and streaked the agar plate. After incubation, he saw the inhibition zone that appeared on the plate, extending right up to the periphery. Duggar could see this with the naked eye, without the help of callipers. Among the microbes swamped over by the isolate were *Salmonella pullorum* which causes diarrhoea in chicks, *Escherichia coli* which causes kidney inflammation

Aureomycin: With SubbaRow's OK, Duggar secured soil samples, particularly those likely to yield actinomycetes moulds, from all over the world. (Credit: Lederle)

and *Staphylococcus aureus* found in summer boils.

The most heartening news came from the reports on animal tests.

Six guinea pigs were given partially purified broths of A-377 in tests conducted by bacteriologists. The guinea pigs should have died but they survived! This was in contrast to A-491 the other antibiotic about which Duggar was more enthusiastic and wanted SubbaRow to take up. The tests of this isolate were negative. Deaths, not survivals, were reported. On balance, the final picture of the two isolates after tests against tuberculosis in guinea pigs was that A-377 was not protective but not homicidal either. A-491 afforded protection by clearing the lungs of the animals but killed them all the same.

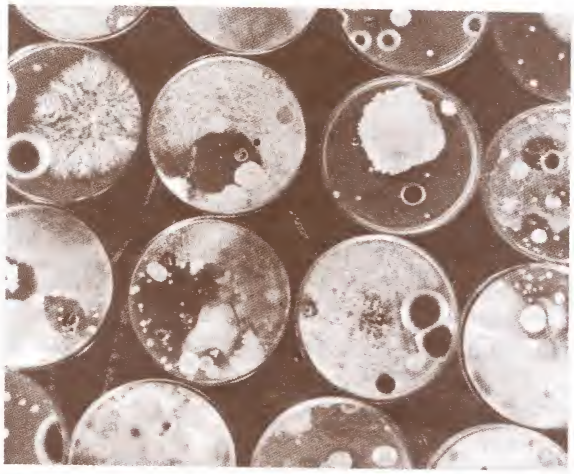
SubbaRow had no second thoughts. He went in for A-377 without delay. And true to his practice of juggling specialists and specialties, he brought in leather technologist Joseph G. Niedercorn of University of Wisconsin for isolating the antibiotic from culture broths.

Niedercorn had problems from the beginning— from June 21, 1946, to be exact. Leather technology had not exactly taught him the techniques of preparing fermentation broths and culture media. He had to learn from doing. And he had to learn at a furious pace to keep the work going. The first problem was over-acidity of the culture medium. For the yellow mould produced too much lactic acid as it grew in the corn steep medium into which it was inoculated. The acid destroyed the mould, and its antibiotic contents. The answer obviously lay in acidifying the medium at a later stage, at the time of filtration, and not in the beginning, by the addition of nutrients such as carbohydrates and nitrogen. But the obvious has a way of eluding even the keenest perception. SubbaRow, too, did not see this.

For a full year and over Niedercorn shuffled around for getting the right compositions for his medium. He collected bucket loads of statistics — to the wrath of SubbaRow. He refused to look at the figures that Niedercorn submitted. He simply X-ed them.

Finally, on February 26, 1947, Niedercorn, in the course of his trials and errors, put some lime water (calcium carbonate) into the medium. A terrific precipitation went up. The yellow mould lived longer and produced more antibiotic. The acid elements got neutralised and the antibiotic reacted with the lime water to form an insoluble calcium salt. The lesson missed earlier (when lactic acid, being produced by the yellow mould, was killing it) was learnt now. The medium had to be acidified at the later stage, when filtration began, not earlier, which was the period of the maximum growth of the mould.

It was the turn of the tide. Yields from filtration were 200-400 micrograms per millilitre of fermentation medium. SubbaRow could well think now of blowing up the operation. By April, some two months later, a pilot plant for producing A-377 was set up in SubbaRow's department. In this he was being wise after the event. He didn't want a repetition of the hassles with production groups that had arisen over folic acid and riboflavin. This time, therefore, he would have



Moulds extracted from soil samples were grown by Duggar on petri dishes: several yielded antibiotics active against a wide range of disease germs. One of them, initially numbered A-377 was chosen by SubbaRow because it fought a broad spectrum of diseases and was moreover safe for clinical trials. This was Aureomycin, the first tetracycline to reach physicians. (Credit: Lederle)

the production work within his department. Soon he switched over to mutant strains of A-377 for producing the antibiotic. In penicillin production, he recalled, big boosts had been achieved by the use of mutants. With the 899th mutant, production went up by two to three times over the parent strain. With the 2920-3 mutant strain, it went up four to five times more.

And now an impasse struck. The isolation and crystallisation of the antibiotic defied all attempts. The whole of the year 1947 was spent in this exercise without result. The project was in danger of being wound up. SubbaRow was fiercely protective of his project, and intensified work along his known unorthodox lines. He brought over organic chemist Charles Pidacks from Maine University, and put him on the job of extracting and crystallising the antibiotic from the wet cake that came from Niedercorn's tanks. And to help out Pidacks, he asked George Krupka, the isolation expert with experience in streptomycin isolation. Krupka applied the same procedure that he had for streptomycin. He used equal volumes of acetone and common salt, and thereby forced the antibiotic into the acetone layer above. The yields went up. Further improvements in the salting procedure were made when butanol was substituted for acetone because of its greater safety. But acetone had greater yields. Butanol was all right for the pilot plant. For larger manufacture, however, new processes that combined safety with higher yields had to be worked out.

Studies in this direction went on. At one stage hydrochloric acid seemed to be the answer. If added to the big amounts of free base got by acetone extraction, it went into solution and could be crystallised subsequently. But acid could destroy the fermentation products too.

And then, quite by chance someone on the job put in a big solid chunk of acid, not the fluid substance, into the fermentation. The antibiotic came out crystallised. But it was not pure. A lot of ash clung to it. Pidacks could not remove it, try as he might.

This was the situation in the year 1947, when the administration tightened the reins. It was a recession year. A ten percent cut in research was imposed. A vice president wanted to call off the entire antibiotic project. Its products were the most expensive and the least marketable, he said.

SubbaRow fought back. None of his workers was to be sacked, he told Bell firmly. They would sweat longer and harder. They would make money for the company. They would make discoveries that were money spinners. He won a reprieve. The company allowed him a say in where the cut was to be imposed. Painful tasks now fell to his lot. He had to terminate the services of valuable old hands, suddenly rendered redundant. The most painful case was that of the gifted, very individualistic Jewish scientist Dr. Werner Lipschitz. Jewish scientists did not easily get jobs in the US at that time. Lipschitz died soon after in tragic circumstances, adding to SubbaRow's feelings of guilt.

Selman Waksman (1888-1973) whose inability, because of previous commitment to Pfizer, to license Lederle to manufacture streptomycin, which he had discovered, challenged SubbaRow to get his own antibiotics, tetracyclines and polymyxin. (Sketch by William Draut in *The Science Book of Wonder Drugs*)

However, to indulge emotions was a luxury he could not afford in his circumstances. If A-377 was not crystallised soon, in two weeks, it was to be written off. Krupka was asked to push himself harder. Krupka did. And luck shone. Within four days he found the answer. It lay in picric acid.

He put the acid in the solution that had ash in it. It joined with the antibiotic and hardened, leaving heavy salts in the solution. He drained off the salts, added dry hydrogen chloride, and got a second precipitate. He drained that off too and got what was the purest antibiotic then. But it was not crystalline yet. Pidacks took over now, watched closely by SubbaRow. Pidacks put the antibiotic precipitate in alcohol. And it crystallised! On assay it had 1,000 units per milligram.

They almost danced with joy. But safety tests remained before the drug could be announced and marketed. The animal tests carried out with 25% pure stuff by the pharmacology group, given orally, were positive. 'Low toxicity and almost no side reactions,' was the verdict of the tests, carried out on 46 dogs, 24 cats, 36 rabbits, 109 guinea pigs, 559 rats, 760 mice and 18 chicks — a veritable zoo.

When not given orally, but given subcutaneously or intravenously, the site of injection and the veins got inflamed. He wouldn't at first limit it to oral administration, for he didn't want to deprive the physician of his five dollar fee per injection; also because he didn't want his antibiotic to be ousted by penicillin, the established favourite of physicians. But A-377 had such a broad spectrum of coverage that it took care of errors in diagnosis. Over prescription posed a problem for some time, as doctors tended to let their guard down in view of its comprehensive character. Vomiting and nausea hit an occasional patient. But nothing more. The dosage was soon corrected and stabilised to the safe one gram a day.

A final series of animal tests were carried out before clinical investigations on human patients began. The animal tests proved A-377 effective against typhoid and paratyphoid germs in mice, and against the erysipelas germ which had killed SubbaRow's only child back in his early immigrant-scientist days. Tested for a number of viral and rickettsial infections induced in mice and guinea pigs, Harold Cox and his associate Sam Wong of SubbaRow's team said that it was ineffective on the tougher virals such as flu, polio and rabies. But it showed good results against viruses of a type of pneumonia in man, and a venereal disease Lymphogranuloma venereum— both resistant to known drugs. It also controlled rickettsiae. These are toxic organisms with a position between viruses and bacteria.

Despite these positive results, SubbaRow was not in any hurry to announce the drug in science journals. Not even to blunt the edge of the announcement by Parke, Davis in *Science* that they had an antibiotic chloramphenicol with chemotherapeutic activity in induced viral infections.

He chartered the clinical investigations of A-377 personally in half a dozen clinics around the country. He was working against a sense of scepticism about the drug that had grown in his

Joe Niedercorn, the organic chemist whom SubbaRow successfully employed to solve the biochemical problems besetting tetracycline production.
(Photo courtesy: Niedercorn)

own medical department. A-377 was no match against penicillin, his men felt. And bearing out their scorn, the results of the first series of tests were all damaging. Test tube trials at Johns Hopkins Hospital showed that A-377 was less effective than polymyxin against gram-negative bacilli and less impressive than penicillin against gram-positive cocci. The doctors said that it was far inferior to penicillin when injected in mice infected with gram-positive germs and to polymyxin in animals infected with gram-negative germs.

It seemed the end of the road for A-377. Years of toil and labour put into its isolation and extraction seemed set to go down the drain. But SubbaRow's fighting spirit woke up as it always did in times of crises. He reasoned that if the anti-viral properties of A-377 in animals, reported by Cox and Wong, could be repeated in humans, the drug could still be medical history and a milestone in the redressal of pain.

He began a fresh round of tests with clinical trials at Harlem Hospital in collaboration with Dr Louis Tomkins Wright. With three associates, Wright tested A-377 for treating the venereal disease Lymphogranuloma venereum (LV), the disease which had proved resistant to penicillin and streptomycin but had responded to A-377 in the tests carried out in animals by Cox and Wong.

The Harlem surgeons administered A-377 to three volunteers. After preliminary studies, they administered it three months later to 22 patients more. The results were astonishing. In four days the bubae in the groin of eight patients shrank. The doctors had not seen such an event in all their 24 years of treating LV. Other patients with rectal inflammation also showed decided improvement within four to eight days. Fourteen cases that were followed for two to sixteen weeks after discharge showed no relapse.

It was 'a million-dollar drug' as SubbaRow put it. 'We are in the money!' he shouted, overjoyed. For he had the answer, at last, to the management's caustic question, what had they got out of the money they had poured into antibiotic research.

More good news came in. The results of Cox and Wong's tests showing A-377's effectiveness in typhus and Rocky Mountain spotted fever were confirmed by research at Texas University. The really heartening piece of news was of A-377's very positive role in curing Q fever. Q fever (Q stands for Queensland, Australia) is spread by wood and cattle ticks. It had broken out in epidemic form in southern and northern California, and was causing rickettsial infections. SubbaRow sent Cox with supplies of A-377, to join a doctors' team in California. Nineteen patients were selected for treatment. Four made no progress. Of the remaining fifteen, fourteen were given the drug orally. All the fourteen regained their appetites in 48 hours. Their temperatures came down in another 24 hours. Eight of them were normal in three days, the ninth on the fourth day, and the tenth on the fifth. One failed to respond even with larger doses.

But the fever could recur. Its rapid termination was no solid proof of cure. The Q viral was known to stage comebacks. It was also

Ledermycin (tetracycline): One of the first derivatives of the original tetracycline, Aureomycin, with molecules tailored to fight new diseases and germs grown resistant to available antibiotics.
(Source: Lederle Catalogue)

known to leave without treatment. More patients, more time and better controlled studies were thus indicated for definitive pronouncements on A-377. So they took two years more and monitored 45 patients. The conclusions were not totally favourable, but not unfavourable either. The verdict was that though the drug was not always effective in Q fever, it had a definite place in its treatment.

One more disease proved responsive to A-377. This was recurrent conjunctivitis or pink eye in which the membrane of the eyelid is inflamed by gram-positive cocci, gram-negative bacilli and an organism related to the flu virus. SubbaRow got tests on 200 patients conducted in Dr Alson E Braley's department of ophthalmology at the Columbia College of Physicians and Surgeons. Dr Braley gave them either intravenous injections of the drug, or directly applied it to the eye, in a half per cent solution of boric salt. All 200 were cured. It was a doubly surprising result for tests on animals for the flu virus had failed.

SubbaRow wasn't yet satisfied. He hadn't yet got an endorsement from Johns Hopkins, whose pronouncements really counted, and where penicillin, streptomycin and polymyxin held full sway. The time seemed apt to approach Perrin H. Long of Johns Hopkins once again, for streptomycin had fallen into disrepute due to many toxic reactions. And he had the result of the Harlem doctors to underwrite his faith. Long was receptive. He was waking to the fact that body reaction to the drug could be different from test tube reaction. This variation got substantiated in many instances, sometimes with other drugs too. A-377 was tested for activity against 186 strains of organisms isolated from patients. It was found active against many which were not only resistant to streptomycin and penicillin but which behaved differently in the test tube. Again, in the glass dish, streptomycin was found to be more active than A-377 against *Brucella Melitensis*, the carrier of the disease brucellosis which is an occupational disease of butchers. But in a human test involving a young housewife, afflicted with the disease, A-377 effected a cure in five days.

With such variations to be kept in mind before a final verdict could be pronounced on this or any drug, more tests of A-377 went on in hospitals all over the United States. Long and his associates at Johns Hopkins tested it against urinary tract infections. They administered it to a 15-year-old girl suffering from a urinary problem from childhood. She was observed for 43 days after admission to Johns Hopkins, and she came down to normal temperature after six oral doses of 100 mgs each. Her urine cultures became sterile. A low-grade fever did, however, develop subsequently as a side reaction. Other chronic patients could not be cured permanently. But it was definitively proved that if treated soon after infection the drug was a curative.

More tests for more diseases and for longer periods were carried out by various groups. Urinary tract infections proved the most susceptible to A-377. In coccal infections, it recorded a definitely beneficial effect. SubbaRow was far from disappointed with the results. The drug had stood up well to the established reputations of streptomycin and penicillin. And in many cases it had outshone them. He was, therefore, ready now for a formal announcement

of the antibiotic to the medical world.

On July 21, 1948, in the Roosevelt Memorial Building of the American Museum of Natural History, A-377 was publicly proclaimed. SubbaRow chose Duggar to preside and make the presentation. SubbaRow was being true to his habit of turning the limelight away from himself. But he expected a similar sense of self-effacement from the person he chose to take the limelight. He had his own rationale for this dislike of playing up individuals. He believed that personality hypes wantonly tampered with the impersonality and namelessness that underlay the growth and formation of ideas. Back in his early years at Lederle, for instance, he had refused to employ a chemist, a thiamine expert, that a New York company was willing to lend him, to help him out in his troubles over synthesising thiamine. The company's stipulation, as we saw, was that the process resulting from their chemist's work at Lederle was to be patented for them by Lederle at its own expense. SubbaRow simply couldn't entertain the proposal. He simply couldn't divide ideas as belonging to Mr X or Mr Y or Mr Z. Ideas had multiple points of origin, he maintained. Nobody could claim sole credit for an idea. That was why he was always reluctant to put his own name down as inventor in any patent application.

The project on A-377 had been piloted by SubbaRow. He had chosen his team. He had assessed each man's capacities independent of his formal qualifications. And he had entrusted the various stages of isolation, fermentation and crystallisation of the antibiotic to men he instinctively knew could tackle the off-beat tasks he set them. He could quickly decide between various alternatives and courses of action. At one stage, for instance, he and Duggar didn't see eye to eye over which strain of the yellow mould was best taken up for further work. Duggar favoured A-406 while SubbaRow was inclined towards A-377. Later, after further research, it turned out that all the six strains being fermented — A-253, 271, 377, 406, 2380 — were of the same species. Duggar's favoured strain could as well have been chosen. But the point is that SubbaRow didn't wait for the verdict from research. He saved time—time that was getting precious by the minute and the hour, for the management was impatient for results—by deciding promptly, which is a true quality of leadership. He was a natural leader in the pathways and terrain of science. But leadership can come into play only when there are men to be led! This principle of relativism working in leadership situations was something he never forgot. He never stopped, therefore, from retreating to the wings when credits for achievements were announced.

Dr Louis Tomkins Wright, distinguished Harlem surgeon who first proved tetracycline's miraculous curative powers. (Photo courtesy: Gertrude B. Stone)

Duggar, however, failed him. To put the team before the self was no part of his thinking. Not that he didn't acknowledge SubbaRow's direction and creative guidance. He could not dismiss it. But he sidelined the contributions of the fermentation and isolation chemists whose skill and perseverance had developed the yellow mould he had discovered into the potent medicine it became. His keynote address at the Conference gave the impression—as it was intended to, no doubt—that he was the discoverer and developer of Aureomycin.

SubbaRow sat in a back row in the auditorium as Duggar proudly and possessively introduced his 'brainchild'. Some of his associates

spoke too, narrating their own experiences in the development of the drug. But Duggar's image as the main actor in the project did not in any way suffer by their accounts. SubbaRow spent his time in the back row discussing with an associate the plans he had for fighting polio and cancer.

SubbaRow died a fortnight later. The broad-spectrum antibiotic era, of which he was the forerunner, came into full swing after his death. Profits were sky high, and with sky high profits came sky high profiteering. Then came squabbles over patents. And, as an inevitable climax, came Congressional and civil proceedings against some of the major drug companies—of which Cyanamid, the parent company of Lederle, was one—for price rigging and monopolistic trade practices.

Five companies were the main characters in the sordid drama of price rigging. Pfizer was the first to bring out a second tetracycline in 1950, after Aureomycin. It was Oxytetracycline. Cyanamid, of course, had Chlortetracycline christened Aureomycin. Both were broad-spectrum antibiotics and had a fast growing market which helped the two companies to make huge profits. This went on till 1953, when both companies simultaneously produced a tetracycline without the extra atoms that marked Chlor-tetracycline and Oxytetracycline. It was also therapeutically superior. But its advent brought a rash of patent hassles. Both companies filed patent applications. Alongside these were two more manufacturers, Heyden Chemical Corporation and Bristol. Which of the four was to get the patent? Pfizer, apparently, because its application had come in earlier. Pfizer, in turn, licensed Cyanamid, to sell tetracycline. Cyanamid bought out the antibiotic division of Heyden. That left three in the field, Pfizer, Cyanamid and Bristol. Pfizer was forced by Bristol together with Squibb and Upjohn to issue selling licences to all the three of them. The five companies—Pfizer, Cyanamid,

Aerial View of Lederle Laboratories in the 1990s. Profits from the sale of SubbaRow's tetracyclines financed the growth of American Cyanamid into a chemical giant that developed new product lines, acquired profitable plant lines and by 1970 ran 90 plants worldwide, had 36,300 employees in its eleven major divisions and with $1.1 billion sales ranked 107 on Fortune 500 and ninth among U.S. chemical companies. Cyanamid sales rose to 4.28 billion by the time it was acquired in 1994 for ten billion dollars by American Home Products Corporation in a hostile take-over. (Photo: Lederle)

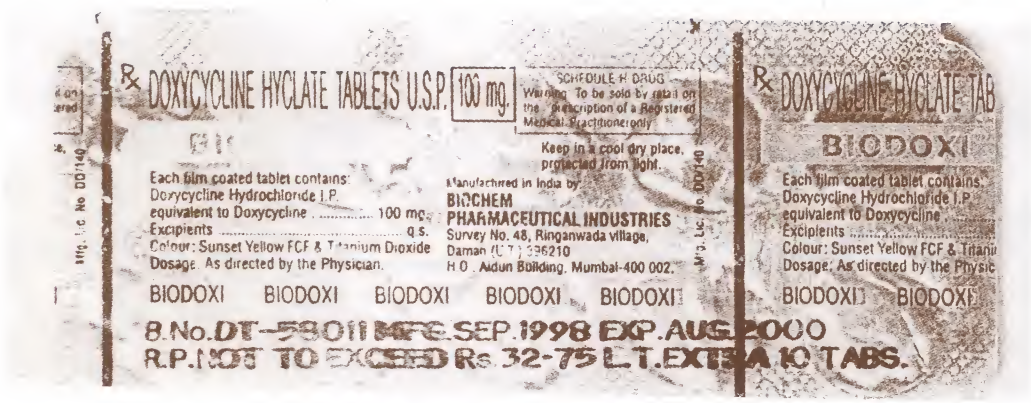
Bristol, Squibb and Upjohn—cornered the market among them, kept prices high and became giant trans-nationals. They cleared themselves of the conspiracy charges in a re-trial they managed after conviction and fine by a New York jury. Civil cases against the companies on charges of fraud for patent monopoly dragged on for many years. India was among the eight foreign countries suing the companies on behalf of their nationals. The companies paid settlements exceeding $250 million, a mere fraction of their extra profits. But most victims including the Third World poor got no relief because the US Supreme Court ruled against foreign governments stepping in to protect their nationals.

Some price cuts were made by the five after some sustained antitrust investigations. But real relief to the public came only after the expiry of the patent in 1972 clearing the field for other firms and smaller companies to make tetracyclines.

Tetracyclines paid SubbaRow's debts to his motherland anew in 1994 when, at the beginning of his centenary year, plague broke out in Gujarat and Maharashtra. They helped confine and eradicate the epidemic. Aureomycin had been sent soon after its release in 1948 to the Haffkine Institute in Bombay (now Mumbai). There Dr Sahib Singh Sokhey was able to save nine out of ten experimental animals suffering from septicaemia caused by the plague germ. After Aureomycin proved itself in a plague case in the American state of Arizona, it was tried in 1951 in Latur, a hyper epidemic plague area then in Hyderabad but which became part of Maharashtra later in the reorganisation of states. Of the 15 plague victims treated by Dr K Ramachandran at the Isolation Hospital, 12 were cured and discharged. The other three had been brought in a serious condition and the drug had no time to act. Tetracyclines were therefore ready for the 1994 plague epidemic at Latur and Surat.

The easy access to tetracyclines in general and the new conquests including malaria that they are making with the evolving of daughter and grand-daughter tetracyclines, of which Doxycycline is now the physician's choice, are of course the best rewards that SubbaRow could have wanted if he had lived.

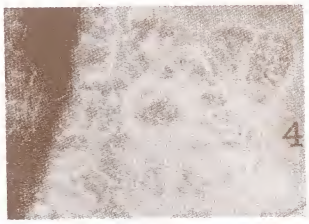
Clifford Hesseltine, member of one of his research teams, gave SubbaRow's name to a new fungus he found in the filter beds of Pearl River's water disposal system. He called it *Subbaromyces splendens*. It was the best form of immortality he could give SubbaRow. Another species of this fungus was subsequently found on the campus of Osmania University in Hyderabad, which is now the capital of SubbaRow's home state. Manohara Chary and Ponnuri Ramarao, its discoverers, have named the new species *Subbaromyces aquatica*.



Doxycycline label (photo of medicine strip)

Subbaromyces splendens: A posthumous tribute to SubbaRow from microbiologist Clifford Hesseltine who discovered this new genus of fungus related to penicillia in the filter beds of Pearl River's waste disposal system in 1953. (Courtesy: Clifford Hesseltine)

SubbaRow Memorial Library: The $350,000 concrete building with 30,000 volumes was dedicated on April 22, 1966 in the Pearl River campus of Lederle at a ceremony attended by New York's Indian Consulate and American Medical Association officials. Night librarian at Harvard Medical School in his early Boston years, SubbaRow reorganised the Lederle Library on moving to Pearl River in 1940 with an annual grant of $15,000. He got a supplementary grant of $6000 to buy German books and journals, telling the management: 'If America is the only nation to survive the present chaos, these volumes may be worth two to three times they are now.' (Photo: Lederle)



Subbaromyces aquatica: A new species of the fungus Subbaromyces was isolated in 1967, 13 years after Hesseltine's Splendens, interestingly enough in the capital of SubbaRow's native Andhra Pradesh — from an open drain near Hostel D of Hyderabad's Osmania University campus by Manohara Chary and P. Ramarao of the University's Mycology and Plant Pathology lab. (Courtesy: Prof P Ramarao)

A Born Outsider

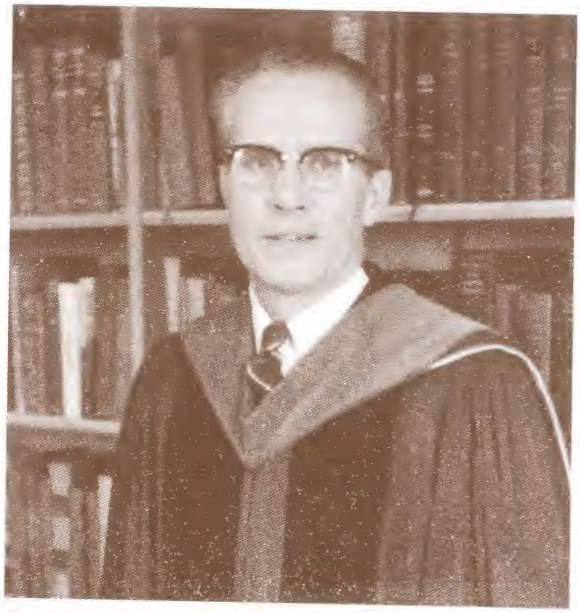
The Emmanuel Baptist Church at Ridgewood near Pearl River. SubbaRow attended Sunday services and supported pastor Torgersen's educational programmes. (Photo: S P K Gupta)

Every Indian who makes a name on alien soil becomes the subject of crass curiosity for his people back home. The curiosity outstrips admiration for his achievements, and gets summed up in the gossipy, yet intense question, 'How Indian was he?'

In SubbaRow's case the answer to this question is basically positive. But so charged is this positive with likely seeming and highly probable negatives that it comes with a disturbing ambivalence. It sounds defensive without intent, for the truths it seeks to convey are floating truths and have not found firm mooring in collective thinking.

One of these truths, which is probably the unifying truth about SubbaRow, is that he had grown above nationality. We can probably comprehend this on a theoretical level. But theory has to be borne out by reality and this does not happen easily in SubbaRow's case. Student visitors from India, for instance, often turned up for face to face meetings with him, to match legend and lore with reality, with facts on the ground.

Invariably he was cold or downright brusque with the visitors. He couldn't pander to such



Reverend Gordon M. Torgersen benefited from SubbaRow's largesse to his church and resorted to dissimulation in using SubbaRow's memory to collect funds for missionary work. (Photo: S P K Gupta)

tourist fancies. Go out and meet Americans, he would tell them. Hadn't they seen enough Indians in India? With one student visitor from his wife's hometown of Anaparthi, all agog for heart to hearts about hard-won victories over alienation and homesickness, he was so distant and polite that the visitor vented his spleen by a typically catty remark about the thousands of rupees a year that this great, snooty scientist was making.

Foreseeably enough, with each such cold shouldering and snootiness, his disrepute as an un-Indianised Indian grew. The fact, however, is that anecdotes of a yearning, almost poetic love for the land of his birth, are also to be found in plenty in his life.

There was the incident, for example, of his going into a semi trance on hearing Indian music in a café he'd gone to with a friend. The effect on him was so noticeably strong and epiphanic that the Indian waiters wanted to know who he was, how long he'd been in the country, all in the usual cheap curiosity of Indians for Indians. And inevitably, SubbaRow withdrew into himself, overcome with distaste for their probing.

All feelings and emotions outside the sphere of science were private for him, in a painful, anti-social way. He was among the major contributors to the education programme of the Emmanuel Baptist Church of Ridgewood which he attended on Sundays for a time. His attendance of church services can, of course, be grist to the mill of the nationalist busy bodies whose natural target of attention he is. But how un-Christian and purely circumstantial his association with the church was, will be seen when we examine the event more closely. In the meantime, the fact to be borne in mind is that he wanted his hefty donations to the education programme kept totally anonymous.

SubbaRow's reasons for opting for a particular course of action were always profounder than most people's. This tended to set him apart, somewhat. And this was ironic, for it was a fuller participation that he sought: a participation that was creative and meaningful. He did, for the most, part gain these joys. There is no evidence of his ever having regretted the choices that he made.

But he derived the joys of participation only from a parallel process of non-participation. He had to step back into the restoring waters of the self from time to time and tune in into himself. He had to articulate the products of his self searching. He had to be his own spectator and eyewitness, to fully reap the fruits of participation.

A four-page letter of self-examination and self-baring, thus, precedes his formal association with the Ridgewood Church. It was the first such communication that the church had ever received from a targeted candidate for conversion.

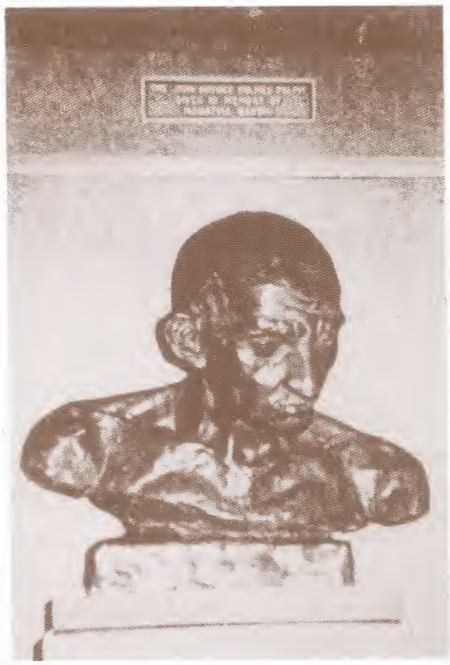
Religion was an internal experience for him, SubbaRow said in his letter to the pastor, Gordon M. Torgerson. It was a slow, piece by piece unfolding of the self within, till the macrocosm

stood encapsulated and entire, on the brow of the probing individual, he said. In the stern, reason-and-proof-based world of science, he went on, there was no place for the sixth sense of inner perception, over and above the five sanctioned senses. As a scientist himself, he said, his endeavour was to somehow accommodate the sixth sense into the field of his working. And he thought he could do this by putting a rein on the sense of ego that his vocation as a scientist gave him.

His reasoning here becomes subtle. It posits a creative, dynamic faith in God in place of a passive, acceptive one. God gave him the intellect to be a scientist, his reasoning goes. But he, with conceit and vainglory, tends to thinks of it as self acquired. To control and stop the growth of this vanity, he has to dedicate his talent to God, the original giver. This task of dedication, and the invocation of the original giver that it demanded to be performed fully, required a setting of community worship.

This reasoning went against his preference for a 'self priesthood', without the mediation of pastor or priest. He admitted this. But a juxtaposition of the two views -- of any two views -- was possible, he felt.

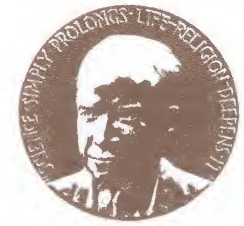
A spirit of inclusiveness had come over him down the years. Perhaps its roots lay in the transformation of his love for Doris McKenzie, a co-worker, into a close, professional partnership. Feelings, emotions and viewpoints had a soft core to them, he was beginning to think. This core was malleable, and re-castable into new formats. Extreme positions of aye and nay were not really warranted, were adolescent fixations, he thought. His readiness for common worship, thus, could co-exist with his inner preference for individual, interiorised worship. Nor did his acceptance of Christ as a spiritual leader bar him from not 'forsaking the great spiritual qualities he had known in his Indian faith', as he made clear to Torgerson.



The John Haynes Holmes Pulpit in Memory of Mahatma Gandhi at the Community Church of New York donated by SubbaRow. SubbaRow became a member of this free church without any formal acknowledgement of Christianity because of his admiration for Christ whose teachings had made it easier for him, as it had for Gandhi, to believe in God 'even in my very active career in science'. The Community Church gives members full freedom of worship and celebrates festivals of all the great religious traditions. (Photo: Ernest Rosenfeld; courtesy: Donald S Harrington)

His belief in Christ was of the same, eclectic kind as Gandhi's, he said, and that it made him no more a Christian than it did Gandhi. He underwent no baptism or a physical ceremony of conversion.

This open mindedness of his does not really seem matched by his eager hosts of Ridgewood Baptist Church. Their creed did not stress ritual. Yet a strong sense of rigidity and exclusivist belief in Christ runs through the avowals of non-denominationalism in the statements of the founder, Dr George W. Truett. SubbaRow did not see the disparity. Or perhaps he did not give it importance. Whatever the reasons, his approach to Christ was inclusive, universalist. His hosts' was, on the other hand, exclusive and centrist.



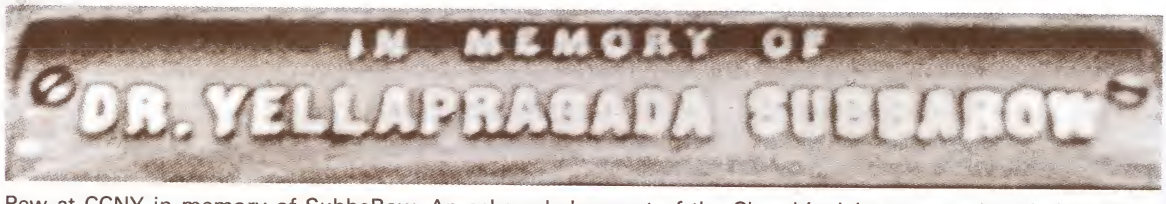
He wanted -- needed -- space in his interior life: space unbounded, unreined by dogma. For him science opened out to philosophy and inner revelations, to astrophysics. The life force, in his view, was an ever-present element coursing through the great void, the vast outer space, ever in search of a propitious activating principle. The planet Earth was one such activating principle, with which the life force impacted, and erupted into life forms. The life force was infinite, unpredictable and unpinnable, he believed. If it was not so, why didn't liquid crystals, so like human cells in every way, have the capacity of reproduction, which was the primary characteristic of living cells ?

These liquid crystals, or coacervates, formed in the ocean, were something of a rage in the biochemical sectors of the thirties. According to Soviet biochemist A.I. Oparin, the process of evolution and natural selection began from some of the coacervates that were better equipped than others in their chemical properties and could thus utilise the organic material of the ocean in a more efficient, superior way. This hypothesis had not yet been proved by the creation of life in the test tube. But SubbaRow could not subscribe to any hypothesis which said that matter preceded mind, generated it, and not vice versa. His philosophical bent and make up rebelled against the notion of a life force contingent on factors outside itself, a force not sovereign, not ever–present and possessed of will.

These fundamental differences between him and his hosts showed up in an unsavoury, unbecoming way after his death.

Torgerson insisted that SubbaRow was a Christian. Not only that. In total disregard of SubbaRow's dislike for ritual, he organised a grand funeral service for him. He exploited SubbaRow's name and his leaning towards Christ. He combined these with his own oratorical skills, and thereby realised handsome sums of money from the assembled mourners as donations for the Church.

This basic lack of a shared line of thought between him and any established order — social or religious or political — showed up repeatedly in his life. It showed up most tellingly in the story of his attempt to get American citizenship. Till 1946 – some twenty three years since his coming to the United States – he was not eligible for citizenship. U.S. laws till then favoured Caucasians and, later on, Chinese residents, in an illogical high handedness towards Indians. Its policy was questioned in vain by sections of the press and Senate members till July 2, 1946. In 1940, when the war years set in, and the Alien Registration Act was passed, SubbaRow was one of the 3896 Indians in the United States, legally required to always carry with them their identity cards and registration numbers and report change of address to the Department of Justice. SubbaRow, in addition, needed special clearance because his position as Director of Research, and the close bearing of his research on the needs of the armed forces on active duty, was considered sensitive. This ham-handed application of the rules to a man and his community whose services to the war effort were freely availed of by the country, was scathingly questioned by the *New*



Pew at CCNY in memory of SubbaRow. An acknowledgement of the Church's debt to one who tried to follow Gandhi: 'No act of mine is done without prayer.' (Photo: Ernest Rosenfeld; courtesy: Donald S Harrington)

Republic: 'The notion that men like these are unfit for American citizenship that is freely granted to the most backward and ignorant Balkan peasant is so absurd that it needs no comments'.

The government lifted the ban on the Chinese in December 1943. A fresh spurt of efforts by India– friendly senators began for similar gestures to Indians. These bore fruit 31 months 'two years and seven months' later, in July 1946, when the Emanuel Cellar Act was ratified by President Truman as PL-483.

SubbaRow was now free to apply for citizenship. He went through the protracted formalities of obtaining all the papers, beginning from the days of his arrival on US soil, some quarter century earlier. This took a year. He got the clearance from the Immigration and Naturalisation Service of the US on July 18, 1947. Now it was more or less straight sailing, though far from speedy. He had to file his 'Declaration of Intent' for getting a 'Certificate of Arrival'. Then, after two years he could have applied for citizenship.

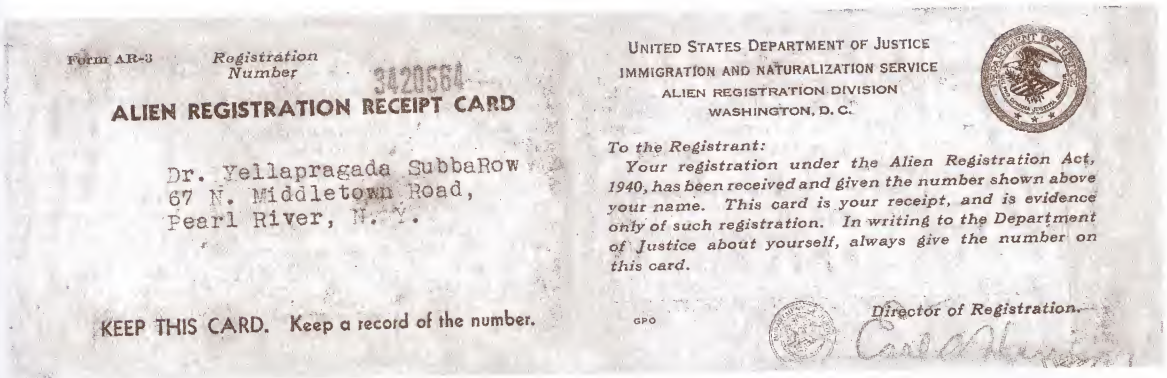
He couldn't have, as things turned out. For he died earlier, in 1948. But the point is that he lost steam. The Declaration of Intent seemed to him a joke in poor taste. The human race, to which he felt bound by ties as old as civilisation, was for him a forum greater than the Supreme Court of New York. He did not apply for it. And he died a citizen of no country athough he did not renounce his Indian citizenship.

This ought to put an end to the question invariably asked of people like him. 'How Indian was he?' It can be answered in two ways. He was fully Indian and fully American: He was neither Indian nor American. He was, in effect, a world citizen. And we in this country have to outgrow our habit of asking the obsolete, boorish question.

His death was sudden, unexpected. He was found dead on Monday, August 9. He didn't show up for an important conference at three o'clock. Nor did repeated knocking at his front door help. It was most unlike him to miss appointments. And he hadn't been in the office, the whole day. An intensely worried Doris McKenzie and her colleagues got the janitor to use the passkey and open the door.

He lay on his bed, dressed in his night shirt and pyjamas. His newspaper and reading glasses lay folded neatly after use on the bedside chair. The light had been switched off in preparation for sleep. He had died without waking.

Death was due to 'natural causes', the medical report unequivocally established, following an



Form AR-3 Registration Number 3420564

ALIEN REGISTRATION RECEIPT CARD

Dr. Yellapragada SubbaRow
67 N. Middletown Road,
Pearl River, N. Y.

KEEP THIS CARD. Keep a record of the number.

UNITED STATES DEPARTMENT OF JUSTICE
IMMIGRATION AND NATURALIZATION SERVICE
ALIEN REGISTRATION DIVISION
WASHINGTON, D. C.

To the Registrant:
Your registration under the Alien Registration Act, 1940, has been received and given the number shown above your name. This card is your receipt, and is evidence only of such registration. In writing to the Department of Justice about yourself, always give the number on this card.

GPO

Director of Registration.

The Alien Registration Card: Despite the valuable part his research direction played in helping the U.S. win the war, SubbaRow was denied American citizenship by a 1940 law that discriminated against those not considered Caucasian. He had to carry this card bearing his right index finger impression, signature and a number testifying to his 'alien' status after a thorough police investigation and a company declaration of his devotion and allegiance to USA. (Courtesy: Lederle)

autopsy. It set at rest wild conjectures of hidden heart conditions; of un-requited love and personal problems leading to suicide; of over-eating, over-working, over-smoking, etc. etc, that whirled around amidst a shocked circle of friends, admirers and well-wishers.

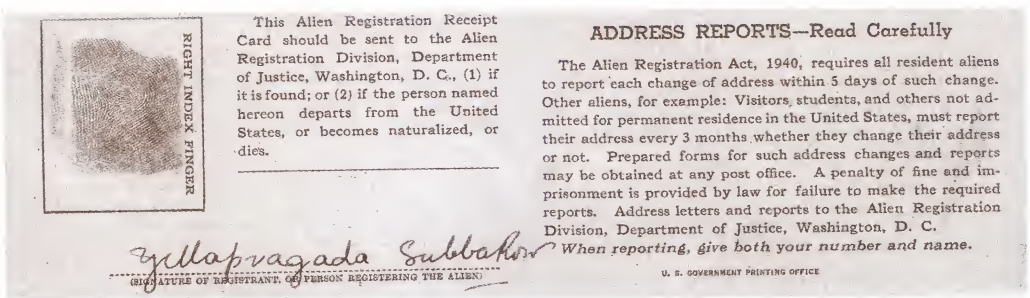
No scars were present on the heart wall. So, hidden heart conditions or unpublicised strokes were ruled out. Unrequited love and nagging personal problems, and suicide in a fit of depression, were just too absurd to be cited as reasons for a man of his character. As for over eating, over smoking and other such indulgences, they had lasted for brief periods, only as reactions to his early years of privation as an immigrant. He had become obese, yes, but he woke to it soon, and became a health freak, a fitness fiend. Overwork could certainly be given more serious thought as a cause. But side by side with over work he knew well enough how to relax. He could unwind fully, sink with adolescent zest into Western movies and cowboy stories, dredging out all the grease and grime of work.

The natural cause that brought about his death was coronary thrombosis. The coronary arteries were choked with cholesterol deposits that had hardened into yellow plaques. Blood could barely pass through them. The left ventricle had worked heroically to pump in blood. But a clot had formed in one of its collateral branches, starving the heart muscles of even the little blood that they had been getting.

The researches he had initiated went on for some time. The guidelines were firm. And the memory of his drive and personality stayed potent yet. Some valuable drugs came out from the efforts of the cancer, tuberculosis and steroid groups. But a horse without a rider has a short run, all said and done. This has been broadly the case with Pearl River since 1948.

Venkamma lived to ninety four, 41 years longer than her son. And she realised fully her dream of being a proud and enviable mother, to make up for the proud and enviable wife her husband had not been able to make her. At first she broke down on hearing the news. How and, why, was it given to her to outlive her son? But the letter from Wilbur Malcolm, Lederle chief, gave her a perspective and some solace. He wrote, following his cable, about SubbaRow's eminence and the vast contributions he made to mankind in the medical sciences. There are many people alive today as a result of his character and genius. Before her death in 1964, she unveiled a memorial plaque to her son at Lederle's Indian plant in Bulsar, Gujarat. Bereavement and fulfilment occurred simultaneously for Venkamma. They did, for Seshagiri too--younger, far younger, exposed to public gossip in the way the mother was not and could not be.

Fulfilment, for Seshagiri, was the fruit of far sterner acts of will, of self-tutoring, and, above all, of silent suffering. Seven years earlier, in 1941, SubbaRow had told her in a fit of anger that he had annulled their marriage and remarried. His anger was the climax to protracted wrangling between him, her, her people and his people, over ways and means of him and Seshagiri coming


RIGHT INDEX FINGER

This Alien Registration Receipt Card should be sent to the Alien Registration Division, Department of Justice, Washington, D. C., (1) if it is found; or (2) if the person named hereon departs from the United States, or becomes naturalized, or dies.

Yellapragada Subbarow
(SIGNATURE OF REGISTRANT, OR PERSON REGISTERING THE ALIEN)

ADDRESS REPORTS—Read Carefully

The Alien Registration Act, 1940, requires all resident aliens to report each change of address within 5 days of such change. Other aliens, for example: Visitors, students, and others not admitted for permanent residence in the United States, must report their address every 3 months whether they change their address or not. Prepared forms for such address changes and reports may be obtained at any post office. A penalty of fine and imprisonment is provided by law for failure to make the required reports. Address letters and reports to the Alien Registration Division, Department of Justice, Washington, D. C.

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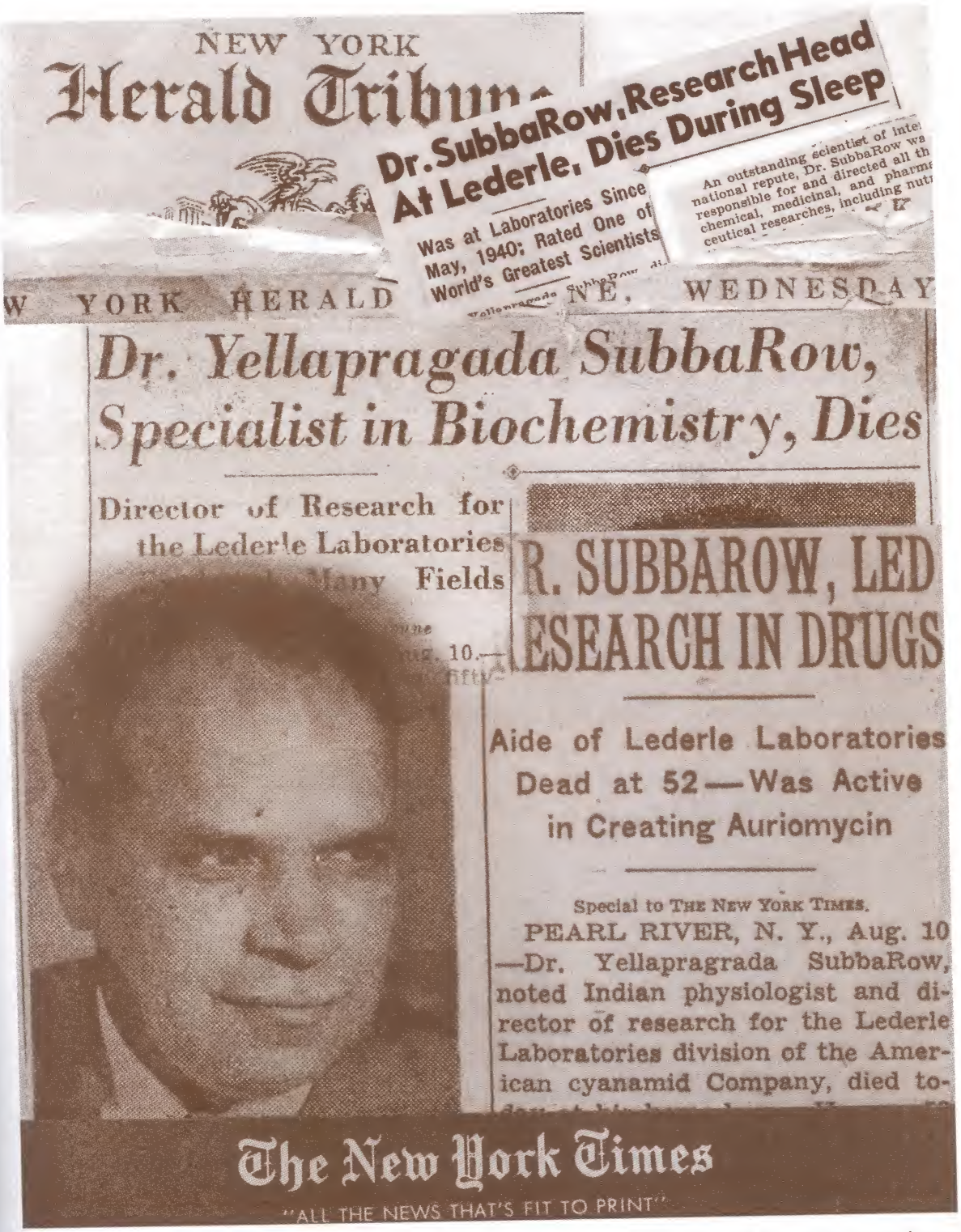


NEW YORK
Herald Tribune

Dr. SubbaRow, Research Head At Lederle, Dies During Sleep

Was at Laboratories Since May, 1940; Rated One of World's Greatest Scientists

An outstanding scientist of inte national repute, Dr. SubbaRow wa responsible for and directed all th chemical, medicinal, and pharma ceutical researches, including nutr

W YORK HERALD ... NE, WEDNESDAY

Dr. Yellapragada SubbaRow, Specialist in Biochemistry, Dies

Director of Research for the Lederle Laboratories ... Many Fields

R. SUBBAROW, LED ESEARCH IN DRUGS

Aide of Lederle Laboratories Dead at 52—Was Active in Creating Auriomycin

Special to THE NEW YORK TIMES.

PEARL RIVER, N. Y., Aug. 10—Dr. Yellapragrada SubbaRow, noted Indian physiologist and director of research for the Lederle Laboratories division of the American cyanamid Company, died to-

The New York Times

"ALL THE NEWS THAT'S FIT TO PRINT"

Death of a Titan: Hometown newspapers note SubbaRow's performance at Lederle and record his reputation as a great scientist. American national newspapers put his research life into perspective, hail him an outstanding medical mind of the 20th Century. (Clips by courtesy of Lederle)

together, setting up home again. He had been carrying on these negotiations amidst a hurricane of work connected with folic acid and the APAF factor. And as always, between wife and work, he found it far easier to relinquish the first, when it came to the crunch.

For seven years, till the advent of the telegram announcing his death, Seshagiri had lived the life of the discarded wife. It is a state that is shadowy and vulnerable both, that stifles speech and hyper-activates thought. When the telegram came, she learnt that she and Venkamma were the next of kin for the money he had left. This meant that he had neither annulled the marriage nor re-married. In a single stroke, then, her life hitherto of virtual widowhood was rendered null and void! She was restored to wifehood, indeed, was deemed never to have been out of that state.

The comedy, of course, was lost on her. It was cruel comedy. Her suffering had been just too sustained and too pointed to send her into dramatic swings of mood, swings at the press of a button, as though she were a mechanical doll. As the reality about her state sank into her, she said in words of mature passion that she was glad that by marrying her he had been enabled to help humanity in the way he had.

His hosts of the Baptist Church of which he was so unorthodox an associate, quietly flouted Venkamma's request that his ashes be immersed in sea or river. When the cremation company brought back the ashes, the urn was taken charge of by Merton Lockhart, a devout Baptist. And as a devout Baptist, he believed that the last remains of a person should never be disposed of. So he held on to SubbaRow's ashes. He held on to them to the end of his days. Lockhart insisted that SubbaRow was a Baptist. Else why would he have been attending the Ridgewood Church? Against this kind of thinking SubbaRow himself would have been stumped for answer. With no relatives around to press for proper last rites, Lockhart's apartment in Ridgewood was where his ashes rested for many years.

But SubbaRow is more than his ashes, of course. He is a life saver, in effect a life giver. Each time a life is saved by any of the drugs he created, he lives again, in innumerable rebirths.

SubbaRow in his Aeronca with flying instructor Clyde Ervin on grass. SubbaRow wondered if flying would improve his muscular coordination and give mental relaxation. After a year of instruction, he made his first solo flight from Wurtsboro (New York) Airport on 28 September 1946. Two days before death, he flew the Aeronca with Ervin over three states taking off from and returning to Spring Valley, seeking relief from tensions of research and administration. (Photo courtesy: Clyde Ervin)

Yellapragada Venkamma at the dedication of Lederle Pharmaceutical Plant at Parnera (Bulsar, Gujarat) talking to American Ambassador George Allen with V R Swamy interpreting. The honour to his mother was a token of the gratitude Lederle felt for SubbaRow who devised drugs that made it a pharmaceutical giant. (Picture courtesy: V R Swamy)

Venkamma unveiling the SubbaRow Memorial Plaque at the Bulsar Plant on May 23, 1953: Tetracyclines made here helped fight the Gujarat and Maharashtra plague in 1994 during the Birth Centenary Year of SubbaRow. (Picture courtesy: V V Sharma)


SCIENCE · SIMPLY · PROLONGS · LIFE · RELIGION · DEEPENS IT

One Hundred Years of SubbaRow

The Plaque in the Pearl River campus of Lederle Laboratories : The words are inspired by SubbaRow's explanation of his interest in theology: 'Being a scientist is discouraging at times. We only prolong life – we don't deepen it.' (Photo: Lederle)

"The panic," reported *INDIA Today* correctly, "evaporated almost as fast as it had struck."

The panic struck India in 1994 as some 5000 suspected cases of plague were reported, mainly from Maharashtra, Gujarat and Delhi, but from almost every state from Punjab in the North to Andhra Pradesh in the South, from West Bengal in the East to Rajasthan in the West. But in sharp contrast to epidemics of earlier times, the killer disease was contained and wiped out in just three weeks, with 56 of the 263 confirmed cases succumbing to it.

If the plague bacillus did not win this time round, although it did exact a terrible price in human suffering and economic disruption, it was not the public health administration that had triumphed. "The real hero", as the newsmagazine declared, was "tetracycline"!

It was India's good fortune that the antibiotic which came out of Yellapragada SubbaRow's laboratory four decades earlier was in sufficient supply although many were pronouncing it redundant because many disease organisms previously susceptible were developing resistance.

Yersina pestis had not acquired immunity to tetracyclines, which did their work with half a million capsules distributed in Surat alone.

SubbaRow in his birth centenary year thus did pay his debt once again to Mother India almost fifty years after death.

The news that tetracycline was SubbaRow's gift to humankind thrilled India. The government issued a postage stamp commemorating his Centenary. The Media were full of stories about the Unsung Hero of Science. And the Centenary Celebrations acquired a new significance.

The SubbaRow Centenary Celebrations were planned and launched long before the plague and the media hype about tetracyclines, thanks to the inspiration provided by a popular science journal's profile of 'one of the greatest medical minds of the Century' to Dr Ram Bahadur Singh, an innovative cardiologist of Moradabad. Dr R B Singh first held on October 6, 1993 at his remote hometown in Uttar Pradesh a SubbaRow Memorial Symposium as part of a satellite meeting of the 4th World Congress on Clinical Nutrition and gave away SubbaRow Memorial Awards to investigators who presented papers adjudged to be the best three. He then canvassed his medical colleagues in Delhi, particularly Dr S S Rastogi and Dr A K Agarwal, for a pre-Centenary symposium in the national capital for young scientists to present papers in the fields where SubbaRow had made his contributions. Kotla Vijaya Bhaskara Reddy, Chief Minister of Andhra Pradesh, was impressed, sanctioned a munificent government grant and flew down to officiate and inaugurate the New Delhi ceremonies. Part of the Symposium's savings were used by the A.P. government to install a bust of the great son of Andhra at Hyderabad's Nizam Institute of Medical Sciences to mark the state-wide centenary celebrations it organised in medical colleges.

A National Committee for Dr. Yellapragada SubbaRow Centenary Celebrations meanwhile came into being with Giani Zail Singh, the seventh President of India, as chief patron because of the initiative of G V G Krishnamurty and Dr S Sriramachari. Representatives of the Indian National Science Academy, INSA, Indian Council of Medical Research, ICMR, Medical Council of India, Departments of Science and Technology, and Biotechnology of Delhi University, Directorate General of Health Services, Institute of Pathology and the All India Institute of Medical Sciences were associated with the National Committee. The Committee mounted a scientific seminar at the All India Institute of Medical Sciences on the morning of January 10, 1995, held a public function of homage at the Mavalankar Auditorium on the evening of January 12 and hosted the release of the SubbaRow commemoration stamp by the Vice-President of India, K R Narayanan, on December 19. It used part of the funds it saved to endow a Memorial Lecture to be awarded, with an honorarium of Rs.25, 000, once in three years by INSA to a pioneer in biomedical sciences. The first lecture was awarded to Prof N R Moudgal, Professor in the Centre of Reproductive Biology at Bangalore's Indian Institute of Science who presented his research on male contraception at INSA on 16 March 1997. The National Committee provided the Indian Academy of Sciences in Bangalore a set of Dr SubbaRow's scientific papers for inclusion in the publication of his collected works it undertook which, alas!, is yet to see the light of day.

A photo exhibition on the life and work of SubbaRow was created by N K P Muthu Koya the distinguished artist of the Directorate of Advertising and Visual Publicity (DAVP), and was mounted at the AIIMS and at the Mavlankar Hall celebration of the Centenary. It took a tour of the country in the seven years following.

It was first taken by Dr K Kannan, the biotechnologist, to Visakhapatnam for exposition at the 47th Indian Pharmaceutical Congress in December 1995, as its agenda included a slot on the 29th for homage to Yellapragada SubbaRow

with a lecture, "Eternal Challenges – Diseases and Therapies – Dedication of a Lifetime'.

With the exhibition as anchor, Professor Bangaru Ramesh Babu at Hyderabad's American Studies Research Centre organised, July 10 to 13, 1996, lectures by distinguished scientists, slide shows, screening of popular science films and an essay contest for High School students. A symposium, 'Mechanism-Based Drug Design' was held in conjunction with the Indian Institute of Chemical Technology, with invited lectures from top in-house scientists as well as from the Indian Institute of Science and the Ranbaxy Research Laboratories.

Mumbai, with a Citizens' Committee of which V V Govardhan Rao was the key member, hosted the photo exhibition at Sachivalaya Gymkhana from January 12 to 14, 1997. Vithal Nadkarni's front-page focus in *Times of India* on the lives saved from plague drew to the exhibition a steady stream of people who had benefited from, or known beneficiaries of, SubbaRow's vitamins, antibiotics, anti-cancer and anti filarial drugs.

Tulsidas Dasappa, Gandhian social worker, invited the photo exhibition next to Bangalore where V Srinivasa Raju of Navachetna Trust arranged around it a series of lectures and slide shows at the Bharatiya Vidya Bhavan and a number of medical institutions in the city from June 9 to 14, 1997.

The photo exhibition then moved to Calcutta where the Andhra Association, thanks to ex-pesident Farida Hussain, mounted the show on June 21 and 22 with top medical scientists of the city as guest speakers at the inaugural function.

The last call of the centenary exhibition created by Muthu Koya was Chennai, the city which had helped SubbaRow find his *paramartha* or prime motive in life and trained him for his mission. A campaign by Mangalam Swaminathan got the University of Madras, which had somehow lost track of its most illustrious son, to celebrate the centenary on July 9, 2001, almost seven years behind the rest of the nation. The enthusiasm of the university administration, faculty and students made up for all the delay, and the inaugural was highlighted by the presentation of Suman Kapur, the biochemist, on data which promises a diagnostic tool for prostatic cancer based on the Phosphorus Method. The day after its inauguration on the university's Guindy campus, the exhibition moved to the nearby Periyar Science and Technology Centre where for four days, from the 10th to the 13th of July, it attracted thousands of school children from all over Tamilnadu visiting Chennai on organised excursions to the adjoining planetarium.

While Koya's exhibition panels remained in storage at the University of Madras for two years before the exposition, Ravi Narain created a new set for display at the annual conference in New Delhi of the Association of Physicians of India (API) in the last week of January 2001. Physicians from all over India got sensitised to SubbaRow's key role in getting the medical profession effective weapons to fight such a wide range of ailments against which they had been, previous to him, so helpless.

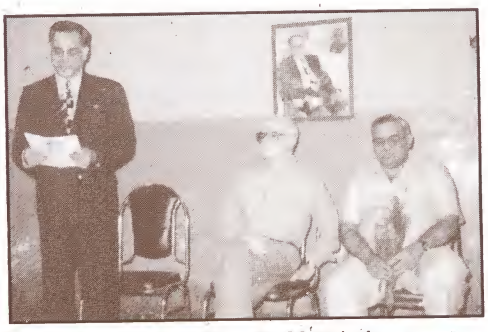
A year later, on January 12, 2002, the 107th birth anniversary, Dr Kannan, now Dean of Biotechnology at the new Indraprastha University in Delhi, decided to bring home the centenary exhibition whose national tour he had initiated. Since Koya's panels had aged and been dismantled after the Chennai exposition, it was Ravi Narain's computer-aided panels that went on display at Indraprastha to complement the day-long symposium. The topic was appropriately biotechnology of which SubbaRow was a forerunner with phosphorus nucleotides, which had to be re-discovered by others because he could not publish them from Harvard. Indraprastha's first Yellapragada SubbaRow Memorial Lecture was by Asis Datta, Vice-Chancellor of Jawaharlal Nehru University : 'Nutritional Genomics:

One Hundred Years of SubbaRow

Centenary Stamp Released by Vice President of India

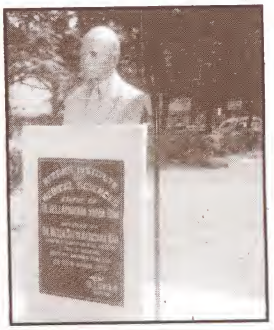
Centenary Eve Seminar at Delhi opened by Sri K Vijaya Bhaskara Reddy

Centenary Celebrations begin at All India Institute of Medical Sciences, New Delhi



Centenary Celebrations in Mumbai

Centenary Celebrations at Chennai



Bust of SubbaRow at Nizam Institute of Medical Sciences, Hyderabad

Commitment to Society'. Young students of Indraprastha University followed him at a seminar, "Excitements in Biotechnology" with papers testifying to their training on the very frontiers of the newest science.

SubbaRow no more an unknown or unsung hero of science, not in his motherland at any rate. The long-drawn-out centenary programme, the media and public response as well as the plethora of newspaper and magazine profiles in English and all the major languages of India barring Malayalam, and analytical pieces in medical and science journals ensured this. Also an abridgement of *IN QUEST OF PANACEA*, the biography of SubbaRow, was published by the Andhra University in a Telugu translation by R V Rao, and by Kannada Pusthaka Pradhikara in a Kannada translation by Dr H D Chandrappa Gowda. Besides, the organising committee of the original 1994 Memorial Symposium has taken up the publication of a Hindi translation by B K Misra, and the present album in pictures and words has been taken up by Vigyan Prasar.

There is nevertheless a palpable sense of dissatisfaction among SubbaRow's admirers in the scientific community and among the public at large that a Bharata Ratna has eluded him posthumously as had a Nobel in his lifetime.

Meanwhile there is no stopping the juggernaut of SubbaRow's virtual panaceas, folic acid, methotrexate, tetracycline and DEC. There is no end to the ever new miracles being performed by the miracle man's miracle drugs. The new 21st Century conquests by his 20th century remedies are reported every now and then. The latest report by medical investigators, in the second quarter of 2002, is that folic acid has proved to be a male fertility drug.

SubbaRow would have considered these rewards to be fulfilling enough, although they would not have induced the medical warrior to retire from his battles against the diseases which still afflict humankind!

A Scientist's Credo : Two Letters

1. To Mr. Kastury SubbaRow, Anaparthi, India

25 Wigglesworth Street

Boston. Mass.

circa 1924

My dear SubbaRow:

Your kind letter to hand. I expected a letter from you long ago. I am glad you have written at last. More glad to hear that you are now able to stick on to a line. That is most promising. I hope you will finish the other three years also soon.

I heard that a Government Ayurvedic College will be opened. I have not heard of any regulation of it as yet. We can look after it when it is certain it will be opened. As I told you before, Ayurveda will come into prominence. Our trials should be to know if it is scientific or empirical.

I am glad you all enjoyed that august body, the Congress, that I could not attend but it does not matter.

What instructions can I be giving you? I do not know. The only thing I can tell you is: gain knowledge. Do not think of how much you will be paid for the amount you have read. It is the worst blunder you can commit. That is what all Indian students do. Do not fall into the same pit. You are given enough to live... You need never fear starvation. So read and gain knowledge. Be a thorough master of Ayurveda by the time I return. I promise you I will make you know more of English medicine – not surgery – more than an M.B. But this promise holds good only if you do not think of money. Knowledge has no price; it is not commercial. If you are paid by the way you can take it and spend it to improve others' knowledge. Do not think of money till you finish your education. People make the mistake that I am studying for a big salary. If I am offered a post with a great amount of time for my laboratory work in a well equipped laboratory for Rs. 150, and another for Rs. 500 with no laboratories, I will accept the Rs. 150 one surely. You wanted to learn from me. Learn this first.

You wanted to learn from me much. Of all men, from me. Let me tell you that my shortcomings and weaknesses are many and innumerable but the only fortunate thing is I know them all. What I ask of you is: subject yourself to self-examination every day. That will serve you a good deal. If you become angry with another, sit down and think why you are angry. What will you do if you are in the other man's position? Have other persons any obligation not to make us (people) angry? In short, analyse the cause of your anger and you will find you are in the wrong

and not the other man. Suppose you examine the other man who irritated you, you will be happy. And if you did not, the spirit of vengeance will be disturbing you. There will be no happiness. If you become irritated, it is you who will suffer and not the other party. This is only an example. Think of everything you do: whether you behaved properly towards others, did you treat them as human beings. In short, make the self examination of yourself at every act. I do not say I have succeeded. Far from it, but I am trying to do it.

As for your nuptials, my dear sir, what can I advise you? I do not know what to tell you. I will write to you what I did. Think of it yourself.

In my Inter class, I began to analyse my life. I wanted to have one prime motive of life which was to guide all my actions and which should be always in my view, and everything I do must be to help it. You must work untiringly for it, and if you fail once or twice in your attempts, you must think that failures are stepping stones to success.

The prime motive may be of any variety. Say, 1. To help your country politically. 2. To help humanity by treating people free. 3. To receive the highest knowledge with a view to helping humanity. 4. To earn vast wealth like Henry Ford. 5. To be a religious monk always thinking of God. 6. To live a peaceful contented life with no children and a nice wife. Etcetera.

The prime motive must be such that it will cover your life and must satisfy the important cravings of your life. Suppose you love women and want to become a monk for fame, it is impossible. You will be a wreck in life. Or you want a peaceful life and great riches, it is impossible.

So by self examination, find out what it is you crave for, what is in your innermost heart and take it up as long as it is not harmful to others. If you choose a wrong one for temporary greatness, to be appreciated by others, you will be a failure. You are not a political man. You gave up your school in emotion thinking you are wanted by the country. You failed. You do not crave for politics. That it is not yours is plain. Your Peddaraju had a greater inclination though in a passive way.

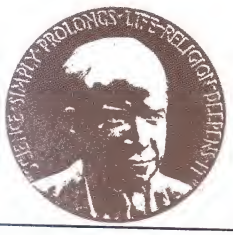
Then, you have a number of secondary motives which will help the primary ones. If you want to be a political worker you do not want to be a fool like Gupta or others who brag about it. You must be a Gokhale or a Tilak. That must be the aim. Or a Konda Venkatappiah at least. It is not difficult. For that the secondary motive: 1. Knowledge of politics. 2. Constitutional history. 3. Capacity to undergo suffering etc. If you want to help humanity by treating people free, knowledge of medicine etc. These are all secondary which vary in your life according to the stages. I can only tell you the secondary purposes if 1 know the primary one.

For example, I will tell you a part of my life. Do not tell it to all others. Because you want to learn from my weaknesses, I am putting them before you.

In my Inter class, after a great deal of consideration, I thought my primary motive is, as the world is an illusion, to become a saint of the Ramakrishna Mission. Evening and morning I walked to Mylapore from Triplicane to the Ramakrishna Mission, learnt the Upanishads, Gita,

Bible under J.S.M. Hooper, Koran; and by the end of Inter class I finished a great deal of religion. I did not care for my classes (at the college). Had it not been for B. Narayanamurty, I would have failed. For fear of him I used to read up my lessons. Mathematics was my favourite subject. But as a member of the Ramakrishna Mission, they asked (me) to take up Medicine. (None knew why 1 took up medicine. They think it was a whim of the last moment.)

There was no more of Narayanamurty troubling me to read up. Though we lived together, he knew nothing of medicine. For my first two years in Medical College, I never attended the classes regularly. My goal was religion and the medical college was only a temporary occupation while I was practicing yoga. I learnt the practices of yoga but I used to think much of religion. The more I thought of Sankara's Adwaita the more (it) appeared to be wrong to me. Bodily objects exist in the senses, Sankara says. (I can't go into details here. I am writing this letter during my short period of rest in the evening.) The theory of Inevitable Destiny began to creep in on me. Meanwhile, the Ramakrishna Mission said unless I take my mother's permission, I can't be admitted.



Listen to me here. Here was my greatest failure in life. 1 thought Adwaita will give me the prime motive. It did not. I chose the wrong one as prime motive.

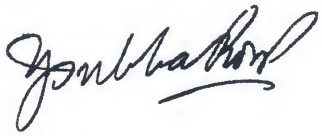
Then my duty lay before the world. In the first two years of the medical course, I was wanting in attendance. There were lot of gaps. My wrong prime motive not only wrecked my religion, it also (wrecked) my education. Then I began to think what my next procedure should be. After a month's deliberation, I concluded that it was knowledge that I sought in religion before of the relation of God to man. I viewed there was no soul but man, a tool of inevitable destiny. I wanted to pursue the knowledge of (the relation of) man to man. I gave up all thought of yoga and began in my third year to work hard for Medicine. Those years I worked harder than 75% of the other students. So those medical students who saw me during my first two years will say I never attended the classes even, and those who were with me during the last three years will tell you that I knew my subjects more thoroughly than many others.

Ayurveda was only a step in my other work. If I had given up my studies during the N.C.O. (Non-Co-Operation movement), I would have been a miserable failure, a life wreck fit only for a lunatic asylum. Then, to improve my knowledge, foreign education was necessary and a good university to learn.

I am coming to your point. There is my wife. I am married. I knew she would attain maturity by the time I finished my course in Madras. So that your people may not come in my way, I always told them, "Three years after maturity", so that I might finish my foreign education. It was not to be. My brothers died. I stopped. Then what next? If I postponed nuptials, my foreign education would go. They wouldn't wait for five years. So I had the nuptials, finished Ayurveda, took her unwilling consent, tried for foreign education and succeeded.

So do you see my weaknesses? Be careful. If your aim is to have a contented home life as the prime motive, give the nuptials every importance. Else, consider what your primary motive is,

what the secondary ones are, and fix the nuptials to suit your main plans. This is the best advice I can give you . . .



2. To Mr. Gordon M. Torgersen, Emmanuel Baptist Church, Ridgewood, N.J.

Pearl River, N.Y.,
March 16, 1948

Dear Mr. Torgersen:

Your invitation to join your church was rather an honour than an embarrassment to me. You see, to me religion is a dynamic subject rather than a static code of established principles. To me, it is an internal experience, a sort of unfolding self revelation piece by piece. Great truths are enunciated by Jesus and Paul: they are succinct, brief and profound. Volumes can be written on some of their statements and each experience gives an extended slant on an otherwise commonplace parable. Here the finiteness of man is shown and, at the same time, the self transcendence of man. Along with it goes an anxiety to overcome the finiteness,

The paradoxes mentioned above can be reconciled and exploited for higher ends by faith in the revelation of the Infinite and in the still greater concept of sacrificial love, or love without recompense, so that one can obtain the tranquillity of spirit and enthusiasm of mind to harness the power of humans to co-ordinate their wills to the will of the Infinite, and lessen the physical suffering of man.

Surrounded in a scientific atmosphere of reason and observation one literally has to struggle to correlate faith, sacrificial love, reason (which by its own nature is limited and finite), and observation, confined to the five senses which refuse to take into consideration the existence of an additional inner sense and are unwilling to take the trouble (Believe me, it is a lot of trouble!) and make them manifest in the everyday correlation of integrated thought. When such a conflict comes, until it clears up, one has to take refuge in Tennyson's words:

"There lives more faith in honest doubt,
Believe me, than in half the creeds."

Mr. Torgersen, this in not an abstract conflict, but is concrete and real (to me at least). At one time it was hard for me to conceive that man acquired an inner spirit and thus became completely differentiated from the rest of nature by his capacity of transcending nature and transcending himself, while science assumed that he is another step in evolution, also in mind. It

was not until I was studying liquid crystals. These have all the physical properties of a unicellular organism but we have to assume that life really did come from the interstitial spaces (Eddington) and somehow entered inorganic materials such as liquid crystals. Thus God introduced complete breaks in creation.

So you realise, Sir, it is a constant evolution of experience for me to realise the inner meaning of Biblical truths. I am so limited, and try so hard to penetrate. The further I go, the more beautiful is the panorama and the more infinite is the depth of Jesus. So I dislike to be bound down by a creed. The only creed I can bow to is sacrificial love. I am afraid that during my lifetime I cannot go one-hundredth the distance Christ asks us to. "I am trying to approach, but I will never arrive." That is, to me, the finiteness of man.

Again, Sir, even sacrificial love is complete only when pride of power, pride of knowledge, and pride of self righteousness disappear. That is easy to say. The freedom of thought of a scientist (which God gave him) is his incentive to creativity and originality, and that is also his worst temptation of the three prides. This is the vicious circle which a scientist suffers from. To dedicate the creative thought to the will of God becomes despairing unless the former is subjected to the discipline of prayer. Thus prayer became very important to me. Even there I am down low in the scale.

I am leading up to the question of self priesthood. In this struggle, an intermediary priest or pastor has no place, and cannot help. These are not things to be argued out or cleared up by analogies; only an inner experience can dispel the fog. Sometimes it looks clear but the next moment the concept (clear a few moments ago) grows hazy and it requires repeated effort to partially at least define its outlines to give a permanent tangibility, though still nebulous.

Let me turn from the abstract to the concrete for a few moments. The Sunday worship is still necessary for the simple reason that an average man can read a literary work understanding every word, but in his average usage he can use only a fraction of the words. For, he never spends enough time to understand the usage of words. The more one reads the more he can master the usage. In Sunday sermons attention is focussed on one single thought of Christ's and thereby brings into consciousness that thought, to be fully explored and incorporated into its proper place in one's philosophy. Sunday sermons are provoking to thought; they are the electron microscope of the scientist. "The new branch only gives fruit."

At this stage, may I answer your feeling of inadequacy in leading us in worship? It is not only the sermon, but also your sincerity and devotion that attracted me there. Sir, there are people who are high in wisdom alone, but sincere servants of Christ's radiate something, and one feels enriched when they are present. Spirituality is really the purifying effect on the environment, in this case, the congregation. That is what you are striving for and that is why you are succeeding, long and tortuous though the path may be.

So you see I am a nebulous visionary, neither perfectly at home with the Bible nor perfectly at home with the test tube. I am too restless to be able to say what my views are or even to

promise they will be my beliefs in the next one year. I have to work them out in my own way, listening to the views of all of you and trying to integrate them into one whole. I suppose even then I will only approach and never arrive.

Now to answer your question:

George Truett once wrote of Baptists: "We hold the immemorial position of Baptists that all true believers in Christ are saved, having been born again, and this without the intervention of preacher, priest, ordinance, sacrament or church. We rejoice in all spiritual unions with all who love the Lord Jesus. We hold them as brothers in the saving grace of Christ and heirs with us of life and immortality. We maintain that the spiritual union of all believers is a reality. This spiritual union does not depend on organisations or forms or rituals. It is deeper, broader and more stable than any or all organisations. We hold that all people who truly believe in Christ as their personal saviour are our brothers in the common salvation, whether they be in the Catholic communion, in the protestant communion, or in any other communion or in no communion."

If this is the spirit in which you invite me, I will be very happy to accept your membership. I believe, as Mr Truett does, in no rituals but only in faith in Christ. Your congregation may not like my unorthodox views.

My letter may be long, but still so brief. I had to sacrifice accuracy for brevity.

Sincerely yours,

Yellapragada Subbarow